AMBULATORY BLOOD PRESSURE MONITORING IN RENAL ALLOGRAFT RECIPIENTS

A dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of

D.M. (Branch – III) (Nephrology)

DEPARTMENT OF NEPHROLOGY

CHRISTIAN MEDICAL COLLEGE, VELLORE

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**AMBULATORY BLOOD PRESSURE MONITORING IN RENAL ALLOGRAFT RECIPIENTS**" done towards fulfillment of the requirements of the **Tamil Nadu Dr. M.G.R. Medical University, Chennai for the D.M. (Branch–III) (Nephrology)** exams to be conducted in July 2009, is a bonafide work of the candidate **Dr.Vinoi George David**, Senior Post graduate student in the Department of Nephrology, Christian Medical College, Vellore under my guidance and supervision. This dissertation has not been submitted, fully or in part to any other board or University.

Guide & Head of Dept.:

Dr. George T. John M.D., D.M., MNAMS, FRACP, FRCP,

Professor and Head,

Department of Nephrology,

Christian Medical College, Vellore – 632004

Acknowledgement

I thank my Almighty God for His grace that provided me good opportunities to learn and strengthen me throughout this study. It is my privilege and honour to extend my respect and deep sense of gratitude to all those minds whose synergistic help and inspiration helped me in completing this dissertation.

I am greatly indebted to Dr. George T John, Professor and Head of Department of Nephrology, whose professional competence, wisdom and scholarly approach to research provided me with excellent suggestions. I express my sincere thanks for his able guidance, moral support and encouragement throughout the project.

I am thankful to Dr. V. Tamilarasi, Professor for her support and help.

I am grateful to Dr. Chakko K Jacob, Professor for his valuable support, care and constant inspiration in all my endeavors.

I am indebted to Dr. Jeyseelan and Ms. Grace R, Department of Biostatistics for their statistical analysis. I express my wholehearted thanks to them without whom this work would not have been completed.

I thank all my colleagues for their unwavering support and help. I sincerely thank all my patients who formed the core of this study, for their kind co-operation. I owe to all my family members whose constant support brought me so far in life.

Contents

ABBREVIATIONS

BP-Blood Pressure

SBP-Systolic Blood Pressure

DBP-Diastolic Blood Pressure

MAP-Mean Arterial Pressure

ABPM-Ambulatory Blood Pressure Monitoring

SBPM- Self Blood Pressure Monitoring

OBP- Office Blood Pressure Monitoring

HBP-Home Monitoring Blood Pressure

ACE- Angiotensin Converting Inhibitors

ARBs- Angiotensin Receptor Blockers

Tx-Transplant

Pred-Prednisolone

Tac-Tacrolimus

MMF-Mycopheonolate Mofetil

Aza-Azathioprine

CKD- Chronic Kidney Disease

CVD-Cardiovascular Disease

GFR – Glomerular Filtration Rate

S.Cr – Serum Creatinine

CysC – Cystatin C

eGFR – Estimated glomerular filtration rate

BSA – Body surface area

List of Tables

List of Figures

ABSTRACT

AIM: To assess prospectively the role of ambulatory blood pressure monitoring with office blood pressure measurement and its correlation with target organ damage in renal allograft recipients of Indian Subcontinent

PATIENTS AND METHODS: Renal allograft recipients were consecutively enrolled to study if kidney transplantation normalizes the BP profile. In this study, the relationship (concordance or discordance) between blood pressure measured by ABPM compared with daytime office BP, and also explored the predictors of diurnal variation, dipping profile of BP and left ventricular hypertrophy in renal transplant recipients. Office and ABPM was done in the pre-transplant, 2nd month, 4th month, 6th month and 9th month was done along with assessment of laboratory and clinical parameters at each time point. The analysis was done using GEE, equivalence study, correlation, multiple linear regression two way ANOVA and kappa statistics for agreement.

RESULTS: 50 renal allograft recipients (M: F=40:10; age 40±11.6 years) were studied. Equivalence study for the comparison of times matched measurements for office and ABPM showed the upper confidence interval of 5-7units the maximum. At each time point the office measurement tend to overestimate the blood pressure by 22-70% for SBP and DBP. Pre-transplant 30% patients were dippers. At 9th month post transplant 40% patients continued to be dippers at the 9th month while another 40% had become non-dippers and 20% became inverted dippers. Among the true dippers only one patient maintained its dipping status throughout the follow up period. Among the true non-dippers at pre-transplant 68%of patients continued to be non-dippers, 24% patients had become dippers and 8% patients had become inverted dippers at 9th month after renal

transplantation. Among the true inverted dippers 66% of patients had become non-dipper, 16.6% had become dipper and 16.6% continued to be an inverted dipper at the 9th month post transplant. Despite a successful renal transplantation and a good control of blood pressure 68% of the patients maintained their non-dipping profile at all time points. Overall, 6% of the patients improved significantly their circadian rhythm; the non-dipping profile from 71.8% at pre-transplant was 69% at 9th month of post transplantation. Most importantly, the dipping profile in this cohort had improved from 12.8% at pre-transplant to 16.8% post transplant. Isolated nocturnal hypertension was 30% which reduced to 2% at 9^{th} month (41.4% of the non-dippers who had nocturnal hypertension at pre-tranplant reduced to 3%). Despite a successful renal transplantation and a good control of blood pressure, 68% of the patients maintained their non-dipping profile through out all the ABPM readings at all time points. There were no predictors for control of blood pressure, circadian rhythm and dipping profile. Predictors for LVM, LVMI and ΔLVMI were duration of dialysis at pre-transplant, post transplant hypertension and number of anti-hypertensive drugs. ($p \leq 0.05$)

CONCLUSION: Majority of the non-dipper dialysis patients maintain a permanently abnormal circadian rhythm, despite successful transplant. The blood pressure was adequately controlled during the post transplant period irrespective of the number of drugs used. Early renal transplant is associated with a highly normal diurnal profile, probably related to tacrolimus and aggressive control of blood pressure. However a longer duration of follow up is required for a significant improvement of the circadian blood pressure and the non-dipping profile.

INTRODUCTION

In renal transplant recipients, hypertension is common and associated with increased cardiovascular and allograft rejection risks. The limitations affecting office blood pressure readings have spurred the development of techniques for measuring blood pressure out of a clinical environment. One limitation is poor accuracy of diastolic blood pressure (BP) estimates, and the ability of this method to provide only a limited number of BP measurements, which can hardly reflect the actual BP load exerted on the heart and the peripheral arterial circulation over the 24 hours. The situation is made worse by the pronounced variability which characterizes BP and by the frequent emotional impact of the physician measuring BP on the reading itself.

The evidence of the marked variability which characterizes BP in daily life and the progressive awareness of the limitations affecting office BP measures have led to the increasing use of approaches able to provide information on out-of-office BP, including the quantification of its variability over 24 h and an assessment of the overall BP load over a given observation period. These techniques include self BP monitoring at home (SBPM) and ambulatory blood pressure monitoring (ABPM).

Though studies of correlation of various modalities of blood pressure monitoring with target organ damage in the renal transplantation population have been studied in the western population, the conclusions have been varied. The ideal blood pressure measurement and its correlation with target organ damage in the long term follow up of hypertension would raise the question of the preferred indicator of overall blood pressure burden and hence the risk for that individual.

OBJECTIVES

1. To study the role of continous ambulatory blood pressure monitoring in the renal transplant population.
2. To study the correlation of office, and ambulatory blood pressure monitoring in the live related renal transplant population.
3. To study the correlation of the various methods of blood pressure monitoring with the graft outcome and target organ damage.

Review of Literature

Epidemiology of Hypertension

In Asia and India

National and regional studies of hypertension prevalence have been reported from a variety of countries in Asia. The reported range of hypertension varies widely, with a prevalence as low as 3.4% in rural Indian Men to as high as 50.1% in Japanese men. However, sampling methods, age range of study participants, and blood pressure measurement methodology differ between the studies, making direct comparisons difficult. Overall, the estimated prevalence of hypertension for men and women, respectively, aged 20 years and older is 22.6% and 19.7% in China, 20.6% and 20.9% in India, and 17.0% and 14.5% in other Asian countries and islands. [3]

Several regional studies have been conducted in different parts of India. However, no national studies have been performed. A recent review on " the global burden of hypertension", the estimated prevalence of hypertension (in people aged 20 years and older) in India in 2000 was 20.6% among males and 20.9% among females and is projected to increase to 22.9% and 23.6% respectively in 2025. Although the prevalence of hypertension was approximately 5% in one rural study, the prevalence in most studies ranged between 20% and 30% in the urban study. Based on these regional data, it was estimated that 60.4 million men and 57.8 million women in India had hypertension in 2000 and projected to increase to 107.3 million and 106.2 million respectively in 2025. [3, 4] At an underestimate, there would be 31.5million hypertensive in rural and 34 million in urban populations. A total of 70% of these would Stage I hypertension (systolic BP 140-

159 and /or diastolic BP 90-99mmHg). Recent reports that borderline hypertension (systolic BP 130-139 and/or diastolic BP 85-89mmHg) and Stage I hypertension carry a significant cardiovascular risk and there is need to reduce this blood pressure.[3, 4] In India and its neighboring countries, awareness level for hypertension is ≤ 45%.[5, 6] In one study the adequacy of blood pressure control and treatment is only 10%. Thus there is a need to increase awareness, detection and adequate control of blood pressure.[7]

In the West

The absolute burden of hypertension in the United States has been estimated to affect 65 million adults, representing about a 30% increase nationwide from 1988–1994 to 1999–2000.[8] The estimated prevalence of prehypertension is 31%, with 39% of adults > 20 years noted to be normotensive and 29% hypertensive.[9] Thus, approximately 47 million individuals in the United States are estimated to be prehypertensive.[10] The percentage of patients with hypertension receiving treatment has increased from 31 to 59% in the same period. However, approximately 30% of adults are still unaware of their hypertension, more than 40% with hypertension are not on treatment, and two-thirds of hypertensive patients are not being controlled to blood pressure levels < 140/90 mm Hg.[12,13]

In Chronic Kidney Disease:

Hypertension presents a unique problem in patients with chronic kidney disease (CKD) since it can act as both a cause of CKD and a significant cardiovascular disease (CVD) risk factor more than 50% to 75% of patients with CKD have blood pressure >140/90 mm.[17] Hypertension in CKD increases the risk of several important adverse outcomes,

including the progressive loss of kidney function leading to kidney failure, early development and accelerated progression of CVD, and premature death.[17] Hypertension results in end-stage renal disease in over 25% of patients requiring renal replacement therapies, second only to diabetes mellitus based on United States Renal Data Systems (USRDS) data.[14] Before the initiation of dialysis, the prevalence of hypertension in CKD patients ranges between 75 and 90%, depending on the nature of the underlying CKD, and uncontrolled hypertension hastens the progression to end-stage renal disease. Hypertension plays a significant role in the high cardiovascular morbidity and mortality rate of all CKD patients, but even mild renal dysfunction leads to increased risks for mortality.[15, 16]

In Transplant Population

Hypertension occurs in up to 60%-80% of kidney transplant recipients. A large registry study showed that recipients with well-controlled blood pressure have improved long-term survival.[17] Smaller; single-center studies also show a relationship with blood pressure control and long-term outcome. Although there appears to be a strong relationship between hypertension and long-term kidney transplant outcome, there are no clinical trials that assess the level of blood pressure control and long-term outcomes.[18-21]

Definition and Classification of Hypertension

Definition: The definition of hypertension by all major guidelines continues to be systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg.[10, 22-27] These guidelines also recommend that individuals with chronic kidney disease or diabetes be treated to a goal SBP < 130 mm Hg and DBP < 80 mm Hg.[10, 22-27]

Classification of Hypertension

It has been suggested that the cutoff for hypertension is best defined as the level of arterial BP at which the benefits of intervention exceed those of inaction.

Over decades the classification has changed as a result of:

- The decrease in the severity of hypertension over the past half century.
- The improvement in the efficacy and side effect profile of antihypertensive medications.
- The recognition of the continuum of cardiovascular risk across all levels of BP.

This has resulted in a gradual reduction in the lower limits of target BP for therapeutic intervention.

Hypertension has been classified based on the new data that has emerged in the last 6years in areas of epidemiology, classification of hypertension and management strategies.[22-26] The final consensus of adopting the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has been accepted in the classification, management and research trials in hypertension.[10] JNC 7 now includes a new designation of "prehypertension" in people

with blood pressures of 120 to 139 mm Hg systolic and 80 to 89 mm Hg diastolic. Although this designation does not provide for a new definition of hypertension, based on data from the Framingham Heart Study [28-29], it does identify individuals with a higher risk of heart disease and stroke than those with blood pressures below this level, and it also identifies those more likely to progress to overt hypertension (> 140/90 mm Hg).

Table 1. Blood Pressure Classification as per JNC VII for Adults Aged 18 Years or Older [10]

BP Classification	SBP mmHg	DBP mmHg
Normal	<120 and	<80
Prehypertension	120-139 or	80-89
Stage I Hypertension	140-159 or	90-99
Stage II Hypertension	≥160 or	≥100

The classification of BP is based on the mean of 2 or more properly measured seated BP readings on each of 2 or more office visits. In contrast with JNC VI report, a new category designated pre-hypertension has been added, and stage 2 and 3 hypertension has been combined.[10] Patients with prehypertension are at increase risk for progression to hypertension; those in the 130/80 to 139/89 mmHg range at twice the risk to develop hypertension as those with lower values.[31]

Table 2: Blood Pressure Classification According to Various Guideline Panels

Classification mmHg	JNC VI [27]	JNC VII [10]	WHO [25]	ESH [23]	Canadian [24]
Optimal	SBP <120 DBP <80	-	-	SBP < 120 DBP< 80	-
Normal	SBP:120-129 DBP: 80-84	SBP < 120 DBP < 80	SBP<140 DBP< 90	-	-
Pre-HTN	-	SBP:120-129 DBP:80-89	-	SBP 130-139 DBP 85-89	-
High-Normal	SBP 130-139 DBP 85-89	-	-	-	-
Stage I (mild)	SBP 140-159 DBP:90-99	SBP 140-159 DBP 90-99	SBP 140-180 DBP 90-105	SBP 140-159 DBP 90-99	SBP > 140 DBP > 90
Stage II (moderate)	SBP 160-179 DBP 100-109	SBP ≥ 160 DBP ≥ 100	SBP > 180 DBP >105	SBP160-179 DBP100-109	
Stage III (severe)	SBP ≥ 180 DBP ≥ 110	-	-	SBP ≥180 DBP≥ 110	SBP≥ 180 DBP≥110
Isolated Systolic HTN	-	-	SBP >140 DBP <90	SBP ≥ 140 DBP< 90	SBP≥ 160 DBP < 90

Circardian Rhythm of Blood Pressure

The circadian rhythm of BP was ultimately established by Millar-Craig et al. using continuous intra-arterial monitoring.[32,33] This study showed that BP was highest mid-morning and then fell progressively throughout the rest of the day; in addition, the study

showed that BP was lowest at night (nocturnal dip), but rose before awakening (morning surge).[33] These findings highlighted the importance of the circadian rhythm of BP with regard to the management of hypertension.[32,34]

Characteristics of the Circadian Fluctuations in BP that May Lead To Harm.

- **Early Morning BP Surge** [32, 37]
    - In the early morning, BP rises sharply in response to the natural activation of the sympathetic nervous system on morning arousal. This early morning surge is also associated with other important hemodynamic and neurohormonal changes, such as increase in heart rate, vascular tone and blood viscosity, and decrease in vagal activity. The activity of the sympathetic nervous system appears to be downregulated during the rapid eye movement period of sleep, whereas awakening selectively stimulates the sympathoadrenal branch of the sympathetic nervous system and increases epinephrine levels.

- **Loss of the Nocturnal Decline in BP (Non-Dippers)** [32,37]
    - The natural circadian rhythm of BP includes a nocturnal decrease of 10–20% in BP. However, in 25–35% of hypertensive patients a 'non-dipper' pattern occurs.
    - **Non-dipping** is arbitrarily defined as present when the night time BP reduction is less than 10% compared to the daytime pressure. This blunted

nocturnal decrease occurs when the natural rhythm of BP is disrupted (for a variety of reasons), both in patients with essential hypertension and with secondary forms of hypertension.

- Clinical investigations in patients with hypertension have associated a blunted nocturnal BP decrease with increased adrenergic and decreased vagal activity during sleep.
- If there is even a significant nocturnal increase in BP **('reverse dippers' or 'risers' or inverted dippers),** a finding that is associated with substantial cardiac morbidity.
- Less commonly, **patients may display a larger than usual (42%); (extreme dippers dippers),** decline in BP during sleep compared with wakefulness; this profile of nocturnal BP has been closely associated with increased white matter ischemic lesions in the brain and an excessive morning BP surge.
- At present, knowledge of the circadian profile of an individual patient (through ambulatory BP monitoring) aids in identifying increased risk.
- At this time, there are no data that show that modifying an abnormal circadian rhythm leads to improved outcomes.

Clinical Implications of the Circadian Variability of BP [32,37]

- The early morning BP surge period is associated with an increase in the incidence of CV events, including stroke and myocardial infarction. Meta-analyses indicate that there is a 40% higher relative risk of acute myocardial infarction, a 29%

increased risk of sudden cardiac death, and a 49% higher relative risk of stroke between 0600 h and 1200 h compared with the rest of the day.

- Loss of the nocturnal decline in BP has been associated with increased risk of cardiac, kidney, and vascular target organ injury compared with patients whose decline in BP at night is normal, 24 and can be independent of the clinic and 24-h mean BP values. Patients with hypertension who exhibit a nocturnal BP increase compared with daytime BP (risers) have the worst prognosis for stroke and cardiac events. However, there is also some evidence that patients with marked nocturnal BP declines (extreme dippers) are at risk of lacunar strokes and silent myocardial ischemia.
- Lurbe and co-workers showed that an increase in night time systolic BP may have a key role in the development of diabetic nephropathy. In contrast, patients were less likely to progress from normalbuminuria to microalbuminuria if their BP decreased during sleep.[38]

Extrinsic Factors Affecting the Circadian Rhythm of BP

- **Effects of Sleep Quality and Activity**
  - The influence of sleep and wakefulness on BP is mediated through cyclic variations of the autonomic nervous system.[39] in the early morning; BP naturally rises sharply in response to activation of the sympathetic nervous system upon arousal. Sleep deprivation increases sympathetic activity and may disrupt circadian rhythm.

- **Dietary influences on the circadian variation of BP**
    - Uzu et al. showed that a non-dipper nocturnal BP pattern can be converted to a dipper pattern in response to salt restriction in salt-sensitive patients with hypertension.[39]

Normotensive subjects may differ in electrolyte handling and regulation during wakefulness, affecting the circadian rhythm of BP. For example, following a period of a high potassium diet, a proportion of normotensive African-American adolescents switched from non-dipper status to dipper status, with a reversal in nighttime BP levels.[40]

Intrinsic Factors Affecting The Circadian Rhythm of BP

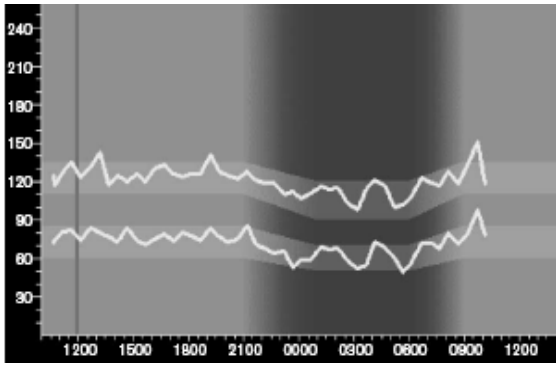
- **Autonomic and Sympathetic Nervous Activity**
    - BP increased independently of activity in neurologically intact patients with lower spinal cord injuries, but not in patients with sympathetic decentralization or higher spinal cord injuries. This sympathetic neural activity may contribute to the regulation of BP over the 24-h period.[51]
    - Higher resting measurements of sympathetic nerve activity were associated with greater daytime BP variability and a more marked nocturnal decline in BP in healthy normotensive subjects.[41]
    - However, some suggest that the existence of the non-dipper phenomenon may not result from disruption of sympathetic neural activity, but from a corresponding decrease in parasympathetic function.[42]

- **Renin-Angiotensin-Aldosterone System**
    - The renin–angiotensin–aldosterone system (RAAS), mainly via production of angiotensin II, is a key regulator of BP. The RAAS is activated in the early morning before arousal as a result of sympathetic neuronal activation. [43]
    - Both renin and aldosterone demonstrate significant circadian patterns in both normotensive and hypertensive individuals, with peak values detected early morning then falling to their lowest point in late evening.[43]

Diurnal Variation of BP and Its Disruption in Chronic Kidney Disease

In the general population, BP falls on average by 10–20% during sleep, a phenomenon referred to as 'dipping'. In about 25% of healthy subjects, and in certain disease states, however, a loss of diurnal variation in BP has been reported (non-dipping). Non-dipping is particularly common in both children and adults with CKD, and an inverse relationship between GFR and the prevalence of non-dipping has been described. The reported prevalence of non-dipping in adults with CKD varies, rates of 50% or higher have been observed at the earliest stages of disease, whereas rates of more than 80% have been observed in patients on dialysis.[43,44]

Diurnal Rhythm Variation in Blood Pressure and its Abnormality in CKD and Hemodialysis Patient



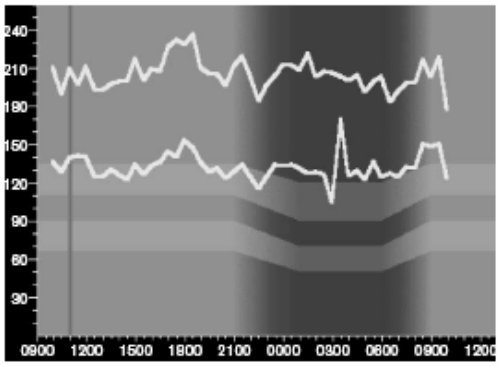


Figure 1: Normal Diurnal Rhythm **Figure 2:Abnormal Diurnal Rythm**

Pathogenesis

Multiple studies have shown multiple etiologies in the raised blood pressure in CKD and hemodialysis patients. No single explanation can be offered for loss of the dipping pattern in BP which is an important predictor of target organ damage in this group of patients.[37, 44-51]

However results and conclusion have been varied. The following etiological factors have been outlined:

a. Volume Status

In non-CKD patients, an association between nondipping and volume expansion has been described. In salt sensitive subjects, who tend to be non-dippers, the nocturnal fall in BP is significantly increased by a low sodium diet.[50] Diuretics can also restore dipping status, as evidenced by an increase in the nocturnal fall in systolic and diastolic BP following thiazide diuretic administration in patients with essential hypertension. [50]

A recent study by Narita *et al*. on 49 hemodialysis patients does support volume expansion as an etiologic factor in the genesis of reduced BP variability.[46] However, the ratio nighttime/daytime BP was significantly higher on the second day. The ultra filtration rate in dippers was significantly less than that in non-dippers and inverted dipper.

In ESRD patients, a statistically significant increase in the night/day ratio and a statistically significant decrease in the awake–sleep difference in BP have been reported from the first to the second day after dialysis. In a study of 71 unselected hemodialysis patients, a trend toward an increased prevalence of non-dipping was also seen that did not reach statistical significance.[52] However, switching patients from thrice weekly to daily dialysis, although effective in reducing BP and extracellular body water, was not found to affect dipping status. A high prevalence of nondipping has also been reported in patients receiving long, slow home hemodialysis thrice weekly.[50] Hence, factors other than volume likely also play a role.

b. Autonomic Dysfunction

Abnormal sympathetic nervous system (SNS) activity has been reported to contribute to the non-dipping pattern of BP in non-CKD patients. In healthy subjects, SNS activity falls during sleep, as evidenced by a decrease in urinary and plasma catecholamine levels and in muscle sympathetic nerve activity (non-REM sleep). In non-dippers without CKD, this nocturnal fall in urinary epinephrine and nor-epinephrine levels is diminished.

Spinal injury patients, patients with autonomic syndromes (e.g Parkinsonism-plus, Shy-Drager), and diabetic neuropaths all have profound alteration in diurnal BP. Uremia is, of course, intimately associated with many neurohumoral abnormalities; in essence, there is relative excess of sympathetic activity. As increased SNS activity has been described in patients with kidney disease, it is possible that loss of diurnal variation in this population is due, in part, to abnormal SNS activity as well.[53-55]

c. Other Factors

These are factors that are known, to cause and or arise as a complication of kidney disease, may also play a role in this diminished nocturnal decline in BP seen in patients with renal disease.

- Diabetes and autonomic dysfunction, operating through increased volume, nocturnal SNS activity, or via other mechanisms, are associated with nondipping and are prevalent in the CKD and ESRD populations.
- Low levels of physical activity during the daytime and poor sleep quality have been linked to a diminished night time fall in BP.[56]
- Sleep apnea, which has been reported in 15% of an unselected group of dialysis patients and at higher rates in dialysis patients complaining of sleep problems, is associated with nocturnal hypertension. In renal patients, excellent studies have shown that obstructive sleep apnea is common and is associated with increased sympathetic drive, nocturnal BP, and also left ventricular mass. It is crucial to establish whether a continuous pressure airway support intervention will successfully reduce these changes.[57, 58]

- A smaller decline in nocturnal BP has also been described in treated versus untreated hypertensives, possibly owing to the waning effect of antihypertensive medications taken in the morning.[59]
- A reduction in arterial distensibility has been related to the alteration in the circadian rhythm of blood pressure in dialysis patients. It is unknown whether the increased pulse wave velocity as documented in a study is at least in part due to increased hyper-cellular volume causing an increase in blood pressure and increased arterial wall stress.[61]

Dynamics of Circadian Blood Pressure Profiles in Renal Transplant Patients

In arterial hypertension cardiovascular complications are only loosely correlated to casual blood pressure. In contrast, 24-hr ambulatory blood pressure measurements have been repeatedly found to be closely related to target organ damage such as left ventricular hypertrophy, hypertensive nephropathy and impaired arterial compliance. Furthermore, 24-hr ambulatory blood pressure measurements allow better detection of trough and peak effects of circadian blood pressure fluctuations. Interestingly, those studies in patients with primary or secondary hypertension in which a circadian pattern of blood pressure was found to be an independent determinant for left ventricular mass also reported an inverse correlation between left ventricular mass and nocturnal declines of blood pressure. Similar findings have been documented in patients after kidney transplantation.

Immediately following kidney transplantation, nocturnal hypertension (‘‘nondipping’’) is common and associated with use of CNIs [60]. Over the long term, the nocturnal blood pressure profile improves in a significant number of patients (up to 30% in some series). The use of cyclosporine post-transplant, however, has been associated with worsening nocturnal pressures.

There is also evidence that kidney transplantation restores the nocturnal decline in BP. In a cross-sectional study of 45 renal transplant patients, Gatzka et al found that with increasing time from transplant, the number of patients displaying a normal nocturnal decline in BP increased. It is evident that the patient inherits the cardiovascular risk of the previous situations that is the time spent on dialysis and chronic renal failure stage.[62]

From above it is clear that the control of arterial hypertension is primordial. ABPM offers considerable possibilities for the study of these patients.

Clinical trials though not numerous offer considerable conclusions. As in dialysis patients the non-dipper status is of high prevalence in transplant patients as high as 92%. The reason for the disruption of the diurnal variation is quite unclear and is a subject of discussion. It is not clear that whether this alteration is the cause or alteration in the renal damage in the grafts. Few authors are of the opinion that the persistent elevation of arterial hypertension is the cause for renal damage while; some are of the opinion that the renal damage is the cause for the persistence of non-dipping pattern.[62]

The underlying renal damage and the immunosuppressive therapy are the cause for the persistence of nocturnal hypertension; even though it is uncertain that the cause for the same has not been understood. Thus, in the first months of renal transplant, there is a loss of normal circadian rhythm and it is after one year more after transplant when dose and number of immunosuppressive drugs are less and the graft is generally is functioning well do the circadian rhythm come back to normal. In cases where the non-dipping pattern exists the functioning of the graft also becomes altered.[62,63]

In spite of adequate BP control as validated by clinic BP recordings, majority of the transplant patients (78.9%) did not have restoration of nocturnal dipping. This is consistent with Farmer's study[63] but at variance with Gatzka *et al*[61] who have reported normalization of BP rhythm, post renal transplant. This conflicting literature on post transplant BP control needs to be addressed by larger trials as untreated nocturnal non-dipping of longer duration may accelerate graft dysfunction.

Hypertension in Renal Transplantation

BACKGROUND

In the pre-cyclosporine era, hypertension occurred in approximately 40 to 50% of kidney transplant patients. The introduction of cyclosporine A has increased the prevalence of hypertension in solid-organ transplant recipients and has been reported in 60 to 70% of adult renal.

In the recently completed 5-year cadaveric kidney transplant trial comparing tacrolimus and cyclosporine, antihypertensive therapy was used in 81% of tacrolimus-treated and

90% of cyclosporine-treated recipients.[64] Although there appears to be a strong relationship between hypertension and long-term kidney transplant outcome; there are no clinical trials that assess the level of blood pressure control and long-term outcomes.

RATIONALE: CKD in Kidney Transplant Recipients

Most kidney transplant recipients have CKD (either kidney damage or GFR <60 mL/min/1.73 m^2 for >3 months). GFR is lower in individuals with a solitary kidney and is even lower in kidney transplant recipients because of toxicity from immunosuppressive agents used to prevent and treat rejection, such as cyclosporine and tacrolimus. However, because albuminuria and abnormalities on urinalysis or imaging studies may not be sensitive to tubulointerstitial or vascular damage characteristic of allograft nephropathy, it is likely that many kidney transplant recipients will not have markers of kidney damage. Patients without markers of kidney damage, but with GFR <60 mL/min/1.73 m^2 will be correctly classified as having CKD. However, patients without markers of kidney damage and GFR ≥60 mL/min/1.73 m^2 may be incorrectly classified as not having CKD.

Hence, post-transplant hypertension is a major risk factor for graft survival. It has not been established whether this is because of the deleterious effects of hypertension on graft structure and function or whether the hypertension is a marker of underlying renal disease. Normotension is a good prognostic marker for long-term graft survival.

The NKF-K/DOQI CKD Guidelines classify kidney transplant recipients without markers of kidney damage and with GFR >60 mL/min/1.73 m^2 "at increased risk of CKD."

Guidelines for the Classification of Hypertension in Transplant Recipients

Guidelines for target blood pressure in transplant patients have been published. As per the NKF-K/DOQI CKD Guidelines the target blood pressure in kidney transplant recipients should be <130/80 mm Hg.[22] ***When compared to other guidelines:***

- The American Society of Transplantation guidelines recommend a blood pressure target of <140/90 mm Hg.
- The British Renal Association guidelines recommend a target blood pressure of <130/80 mm Hg.

Since most kidney transplant recipients have low levels of proteinuria, it was the opinion of the NKF-K/DOQI Work Group that the level of blood pressure control recommended for CVD prevention (<130/80 mm Hg) would be appropriate for slowing kidney disease progression.

In patients with higher levels of proteinuria, a lower blood pressure goal of <120/70 and agents that lower proteinuria may be appropriate, as in non-diabetic kidney disease.[70]

It was the opinion of the NKF-KDOQI [22] that target blood pressure should be <130/80 mm Hg, similar to recommendations in diabetic and non-diabetic kidney disease.

A retrospective analysis of 29,751 kidney transplant recipients with blood pressure values at 1 year demonstrated an increased risk of graft loss with each 10 mm Hg increase in SBP over 140 mm Hg and DBP over 90 mm Hg.[65] In addition, a single-center study of

long-term kidney transplant survivors with a DBP of 89 to 99 mm Hg had a statistically increased rate of GFR decline compared to recipients with lower blood pressure.[72] It has also demonstrated a graft survival advantage for transplant recipients with lower blood pressure readings at 1 year. In another study, the increased risk of graft failure for every 10 mm Hg increase in SBP was 1.15 (95% CI, 1.02 to 1.30) and for every 10 mm Hg increase in DBP was 1.30 (95% CI, 1.05 to 1.61).[74]

Pathophysiology of Hypertension in Renal Transplants

The cause and pathogenesis of post-transplant hypertension is multifactorial. The causes of sustained hypertension after renal transplantation are listed below:

Pathogenesis of Hypertension in Renal Transplantation

The most common aetio-pathogenesis in renal transplantation will be discussed in this review:

a. **Immunosuppression and Hypertension**

Corticosteroids

The mechanism of steroid-associated hypertension remains incompletely understood and is likely multifactorial, involving both expansion of extracellular volume and alterations in vascular tone.

- Expansion of the extracellular volume occurs indirectly in the proximal nephron, where glucocorticoids up-regulate angiotensin II receptors and, therefore, enhance sodium transport. Glucocorticoids exert a more direct effect on distal sodium

reabsorption by binding to mineralocorticoid receptors and glucocorticoid receptors in the distal convoluted tubule and collecting duct. Both effects are potentially modulated by the activity of 11ß-hydroxysteroid dehydrogenase, an enzyme that inactivates circulating glucocorticoids, preventing them from binding to their receptors, and may be deficient in some forms of essential hypertension.

- Several mechanisms have been proposed to explain the alteration in vascular tone. An indirect increase in vascular tone may occur when glucocorticoids bind to glucorticoid receptors and mineralocorticoid receptors on vascular smooth muscle cells, leading to up-regulation of adrenergic, vasopressin, and angiotensin II receptors and a subsequent increase in the sensitivity of vascular smooth muscle cells to catecholamines and angiotensin II.
- In addition, glucocorticoids may induce changes in vascular smooth muscle cell concentrations of sodium, calcium, and, possibly, potassium via down-regulation of the Na-Ca exchanger and/or the calcium-dependent potassium channel, leading to sodium and calcium influx and subsequent vasoconstriction.
- Finally, glucocorticoids may down-regulate the expression, synthesis, and/or activity of circulating vasodilators such as nitric oxide synthase, prostacyclin, and guanylate cyclase activity induced by atrial natriuretic peptide. Glucocorticoids may also induce expression of angiotensin-converting enzyme (ACE) in vascular smooth muscle cells.[75]

Attributable incidence of steroid-related hypertension in renal transplant patients ranged from 2 to 17% over a follow-up period that ranged from 18 months to 8

years.[76] Attributable incidences was calculated by subtracting the incidence in steroid-free patients from the incidence in steroid-treated patients.

Steroids may have a synergistic effect with cyclosporine in causing hypertension. But once the maintenance dose of prednisone has been reduced to <10 mg/day; steroids appear to have little if any role in contributing to the genesis of hypertension after transplantation [77, 78]. Converting from daily to alternate- day steroid therapy while maintaining the same total dose significantly reduces the mean arterial pressure [80]. Steroid withdrawal has been shown to have a beneficial effect on the prevalence and severity of hypertension in children and adults [80, 81.]

Calcineurin Inhibitors

The advent of CNIs (cyclosporine and tacrolimus) has been associated with a dramatic rise in the prevalence of hypertension, particularly in solid organ transplant recipients. The mechanism of CNI- induced hypertension involves renal, neural, and vascular mechanisms that lead to an inability to regulate both volume and renin activity.[82] Cyclosporine and tacrolimus cause functional, dose-dependent, and, typically, reversible renal vasoconstriction, primarily by the afferent arterioles.[83] As a result, increased intraglomerular pressure and a subsequent reduction in the glomerular filtration rate (GFR) lead to sodium and water retention and an eventual increase in blood pressure. Repeated ischemic insults of this type may lead to impaired autoregulatory ability. Among the mediators most commonly implicated in its pathogenesis, endothelin and angiotensin II emerge at the forefront. Other theories include excess sympathetic

stimulation and decreased effects of vasodilators, such as nitric oxide, natriuretic peptides, or prostaglandins.[84]

Cyclosporine may also cause hypertension by its effects on renal nerves. It has been shown that the infusion of cyclosporine into rats increases genitofemoral nerve traffic and causes an increase in sodium retention [88.] Supportive evidence of the role of renal nerves comes from the demonstration that cyclosporine-induced decreases in RBF can be mitigated by the denervation of the kidney or by the α1-antagonist prazosin[77]. The fact that renal allografts are denervated could explain why more severe hypertension and nephrotoxicity occur in nonrenal transplants as compared with kidney allograft recipients.

However, an alternative explanation for the lower incidence of hypertension in kidney transplant recipients may be that kidney transplant programs generally use a lower dose of cyclosporine than is used in non-renal transplant recipients. In pediatric renal transplant recipients, cyclosporine dose requirements are generally higher than in adult patients; this may explain the higher prevalence of hypertension in young kidney transplant recipients.

Non-renal mechanisms may also be implicated in cyclosporine-induced hypertension. Cyclosporine has a generalized vasoconstrictor effect on smooth muscle and may affect the systemic circulation and total peripheral resistance, independent of its effects on renal tissue [78, 79]. Cyclosporine therapy also results in mild hypomagnesaemia which may

contribute to hypertension [89] and may also affect intracellular calcium-binding proteins which may cause increased vascular tone.

In patients with stable renal allograft function and cyclosporine blood levels the degree of hypertension has been shown to neither abate nor increase over a 3-yr study period [78, 79].

Chronic Rejection

In the pre-cyclosporine era, chronic rejection was the most common cause of post-transplant hypertension. This condition is characterized by progressive deterioration in renal function, the development of hypertension and proteinuria and histologic evidence of microvascular and tubulointerstitial disease. CNIs may cause structural, and largely irreversible, injury to the kidney. Chronically, these drugs induce arteriolar hyalinosis, striped interstitial fibrosis, and tubular atrophy, which lead to permanent scarring of the parenchyma, chronic sodium retention, and, variably, proteinuria. The result is a volume-expanded form of hypertension akin to that of chronic kidney disease. The mechanism of this chronic toxicity may be related to increased activity of transforming growth factor $ß_1$, osteopontin, chemokines, or angiotensin II or accelerated apoptosis in tubular and interstitial cells, or it may result from repeated episodes of renal ischemia from acute vasoconstriction.[80-85]

Decreased nephron number is thought to cause sodium-sensitive hypertension, and this may may be one mechanism by which nephron underdosing or early loss of nephrons because of rejection contributes to the later development of chronic allograft dysfunction.[90]

Renal Artery Stenosis

The development of functionally significant transplant renal artery stenosis is characterized by an acute deterioration in renal function in association with the sudden onset of hypertension or deterioration in preexisting hypertension and the appearance of a new bruit over the transplant. Functionally significant renal artery stenosis can be diagnosed by the demonstration of a reduction in RBF and GFR after the administration of an angiotensin-converting enzyme inhibitor (ACEI); however, the use of this test is not valid in patients receiving cyclosporine.

The development of recurrent or de novo glomerulonephritis or recurrent diabetic nephropathy in the transplant may be associated with the development of hypertension; although these conditions are not important causes of post-transplant hypertension.

Renin Mediated Hypertension

Renin-dependent hypertension may be responsible for persistent hypertension in a small percentage of and is likely to persist despite successful transplantation. It can usually be controlled with antihypertensive therapy. But in rare cases; it may be the cause of severe hypertension after transplantation. Diagnosis may be confirmed by a high native kidney-to-transplant renal vein renin ratio. If severe, bilateral native kidney nephrectomy[91] or ablation by embolization [92] has been shown to be effective. It is possible that recurrent or de novo essential hypertension may develop after renal transplantation. However, this is very difficult to document. The influence of native kidneys on post-transplant hypertension usually is attributed to hyper secretion of renin by the native kidneys. Renal

vein catheterization of host and transplanted kidneys has shown hyperreninemia arising from native kidneys, although metabolism of plasma renin activity does not predict reliably blood pressure or the response to nephrectomy in transplant patients.

Likewise, it has been difficult to document an increased prevalence of post-transplant hypertension in recipients of cadaveric allografts from donors with a family history of essential hypertension [77]. However, requirements for antihypertensive therapy have been shown to be significantly higher in recipients of cadaver kidneys from donors with a history of familial hypertension.

Correction of Anemia

Successful transplantation induces a rapid rise in hemoglobin concentration and hematocrit. In patients maintained on dialysis rapid correction of anemia frequently is associated with exacerbation of preexisting hypertension, the mechanism for which is complex but involves a failure of cardiac output to normalize after correction of anemia and may be related, at least in part, to persisting extracellular volume expansion, which helps to maintain oxygen delivery to the tissues in anemia.[90]

Transplanted Kidney

There is increasing evidence that alterations in renal sodium handling are primarily responsible for the genesis of many forms of hypertension and that these abnormalities may be transmitted with the kidney by transplantation, indicating that they are intrinsic to the kidney itself. In humans, there is evidence from the pre-cyclosporine era that pre-exisiting essential hypertension in renal transplant recipients could be reversed by the

receipt of a kidney from a normotensive donor. Retrospective and prospective studies in patients not receiving CNIs have shown that kidneys from donors with family history of hypertension increase the risk of post-transplant hypertension only in recipients who did not have a family history of hypertension. This group of patients (normotensive family, hypertensive kidneys) were at more risk of hypertension and suffered a greater degree of renal damage during acute rejections than all other recipients.[90]

The Different Modalities of Measurement of BP

In the past 30 years, the techniques for measuring blood pressure to determine whether a patient has hypertension have undergone a substantial change. The bulk of our knowledge about the risks of hypertension and the benefits of treating it is based on the traditional method of taking a small number of readings with the auscultatory technique in a medical setting. However, such measurements, which are of enormous value on a population basis, often provide a poor estimate of risk in an individual patient for reasons such as poor technique of the observer, the "white-coat" effect (the transient but variable elevation of blood pressure in a medical setting), and the inherent variability of blood pressure. Two techniques have been developed to improve the estimate of true blood pressure ambulatory monitoring and home monitoring (or self-monitoring) [93]

Availability of accurate blood pressure (BP) measurements is a necessary prerequisite to reliably assess patients with suspected BP elevation or with established hypertension that is to ensure correct diagnosis and management of a high BP condition. It is also an essential step to properly determine the need for antihypertensive treatment and its efficacy, as well as to estimate the risk of developing BP-related complications.

Out-of-office blood pressure (BP) measurements such as home or ambulatory BP provide important information in the diagnosis and management of hypertension and hypotension. This increased use is related to the improved technology of the devices, their relatively low cost, the availability of relevant scientific research, and the patient acceptance of the methodology.[94]

Oscillometry uses small perturbations or oscillations in the cuff that are produced as the artery opens to measure BP. The oscillometric devices do not need a stethoscope or microphone. Aneroid devices use the deflection of a diaphragm within the meter to register BP and generally require a stethoscope.[94]

Office Blood Pressure Monitoring (OBP)

Method of Accurate BP Measurement

The accurate measurement of BP is the *sine qua non* for successful management. The equipment, whether aneroid, mercury, or electronic, should be regularly inspected and validated. The auscultatory method of BP measurement should be used. Persons should be seated quietly for at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is indicated periodically, especially in those at risk for postural hypotension, prior to necessary drug dose or adding a drug, and in those who report symptoms consistent with reduced BP on standing. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least

two measurements should be made and the average recorded. For manual determinations, palpated radial pulse obliteration pressure should be used to estimate SBP; the cuff should then be inflated 20 to 30 mm Hg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mm Hg per second. SBP is the point at which the first of two or more Korotkoff sounds is heard (onset of phase 1), and the disappearance of Korotkoff sound (onset of phase 5) is used to define DBP. Clinicians should provide to patients, verbally and in writing, their specific BP numbers and the BP goal of their treatment.[10] In spite of its proved clinical usefulness, however, such an approach is now acknowledged to suffer from a number of limitations:

(1) Limited accuracy of diastolic BP estimation (particularly in obese patients, in aged patients, in pregnant women, etc.)
(2) Observer bias and digit preference.
(3) Alerting reaction ('white coat' effect)
(4) Overestimation of initial BP
(5) Underestimation of effect of treatment.
(6) Inability to account for BP variability.
(7) Limited reproducibility of isolated office readings. (Regression to the mean phenomenon).

One limitation is poor accuracy of diastolic BP estimates, and the ability of this method to provide only a limited number of BP measurements, which can hardly reflect the actual BP load exerted on the heart and the peripheral arterial circulation over the 24 h. The situation is made worse by the pronounced variability which characterizes BP and by

the frequent emotional impact of the physician measuring BP on the reading itself. The latter phenomenon is responsible for a pressor reaction right at the time when the BP is taken, leading to an overestimation of the actual BP levels, known as the 'white coat' effect. [95]

Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory blood-pressure monitoring was first described more than 40 years ago.[3] The currently available ambulatory monitors are fully automatic and can record blood pressure for 24 hours or longer while patients go about their normal daily activities. Most monitors use the oscillometric technique.

Ambulatory blood-pressure monitoring provides automated measurements of brachial-artery pressure over a 24-hour period while patients are engaging in their usual activities. Ambulatory blood-pressure monitoring can provide the following three types of information, which are of potential value in the clinical field: an estimate of the true, or mean, blood-pressure level, the diurnal rhythm of blood pressure, and blood-pressure variability.

The availability of lightweight, quiet, easy-to-wear automated monitors has facilitated the collection of large volumes of data (approximately 100 measurements in 24 hours) while a subject pursues everyday activities. Data gathered using ABPM have made important contributions to our understanding of the pathophysiology of hypertension and its complications, the definition of daytime and nighttime normotension, the prognostic value of ambulatory BP, and the evaluation of therapy.

Why is ABPM superior to conventional blood pressure measurement?

There are a number of obvious advantages: The technique gives more measurements than office BP the real blood pressure is reflected more accurately by repeated measurements [110-112].

(1) ABPM provides a profile of blood pressure away from the medical environment, thereby allowing identification of individuals with a white-coat response[110-112].

(2) ABPM shows blood pressure behavior over a 24-h period during the patient's usual daily activities, rather then when they are sitting in the artificial circumstances of a clinic or office;

(3) ABPM can demonstrate the efficacy of antihypertensive medication over a 24-h period, which facilitates more rational prescribing than having to base a decision on one or a few office pressure monitoring confined to a short period of the diurnal cycle[110-112].

(4) ABPM can identify patients whose blood pressure does not reduce at night- time the non-dippers – who are at greater risk for cardiovascular morbidity[110-112].

(5) Finally, the technique can demonstrate a number of patterns of blood pressure behavior that may be relevant to clinical management – white-coat hypertension, hypotension, dipping and non-dipping, etc. [110-112].

These advantages should have brought ABPM into much wider clinical use many years ago. However, this eventuality was delayed because, despite a large body of work showing that ABPM predicted outcome on the basis of surrogate markers such as left ventricular hypertrophy, microalbuminuria and arterial stiffness, there was

insufficient prospective evidence to show that ABPM was superior to office BP monitoring in predicting cardiovascular mortality.

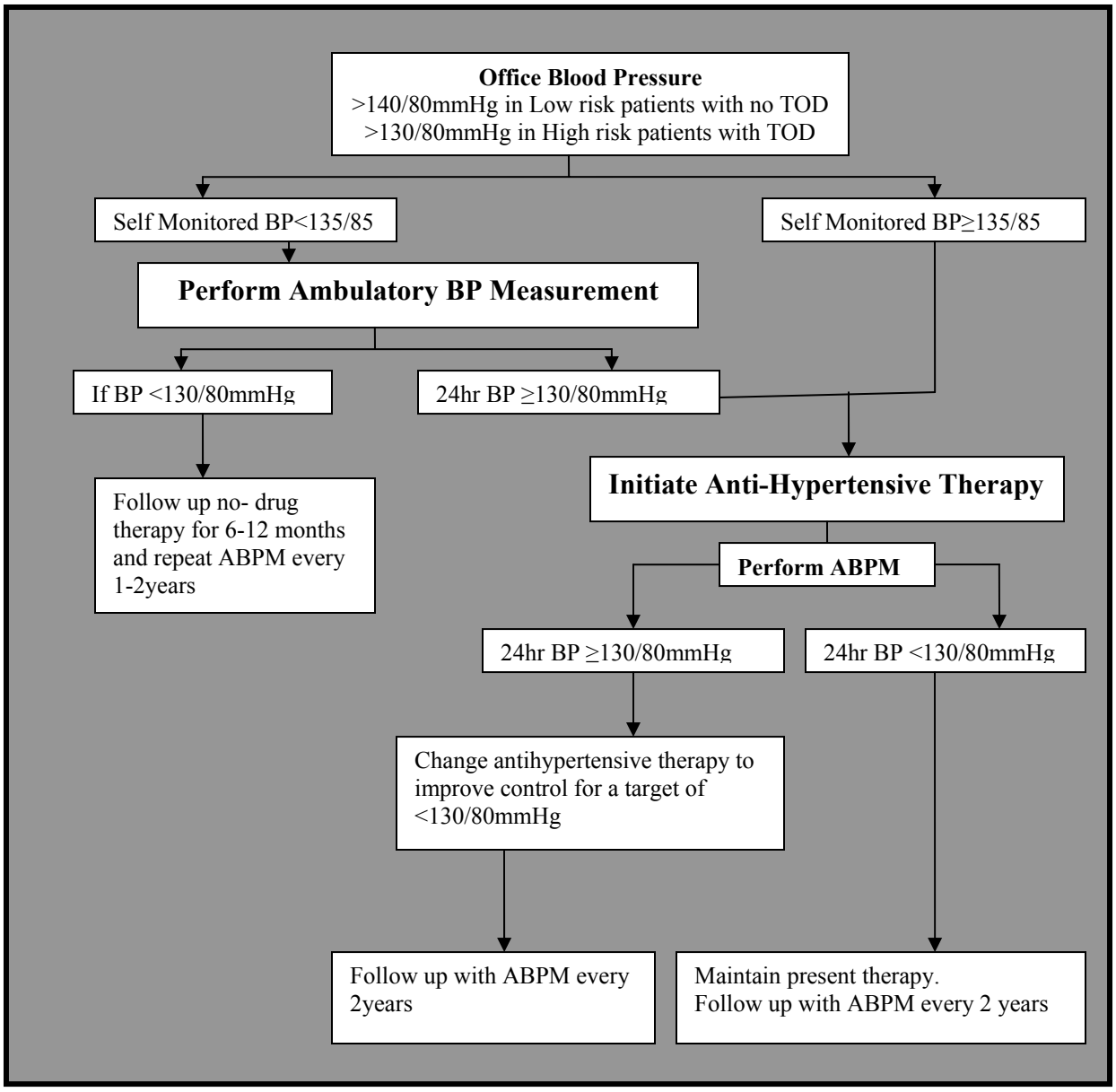
Guidelines for Using the ABPM Machine

- 15-30 minutes needed for educating the patient.
- Patient's details to be entered
- Measure BP in both arms:
    - IF SBP difference is <10mmHg, use non-dominant arm
    - If SBP difference is ≥ 10mmHg, use arm with greater pressure.
- Select the appropriate cuff.
- Select the frequency of measurement
- Inactivate the LCD display
- Give patients written instructions and diary card
- Instruct patient how to remove and inactivate the monitor after 24hr.

In clinical practise measurements are made at 20-30min intervals in order not to interfere with activity during the day and sleep at night. There should be at least 14 measurements of systolic and diastolic measurements during the day and at least seven measurements at night; OR else the ABPM should be repeated.

Use of Ambulatory Blood Pressure in Hypertension Management[113]

Figure 3: Approach to Ambulatory Blood Pressure Monitoring



Self-monitoring of the blood pressure at home and at work can be used to assess whether there is a large disparity between the office and out-of-office blood pressures before ambulatory monitoring is considered. It is likely that many patients whose self-monitored blood pressure is apparently normal will have elevated ambulatory blood pressure and

would benefit from antihypertensive therapy. For those whose ambulatory blood pressure is truly normal (<130/80 mm Hg) despite an elevated office blood pressure and in whom there is no evidence of other cardiovascular risk factors or target-organ disease, avoidance of unnecessary drug therapy would be a clear benefit of the monitoring procedure.[113]

Common Patterns of Ambulatory Blood Pressure Monitoring.[94]

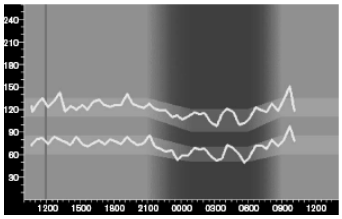


Figure 4: Normal ABPM-This ABPM suggests normal 24-h SBP & DBP (128/78 mmHg daytime, 110/62 mmHg night-time).

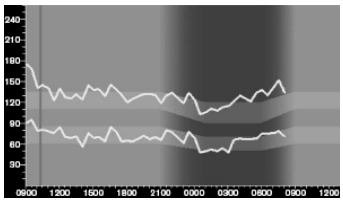


Figure 5: White-coat hypertension. This ABPM suggests white-coat hypertension (175/95 mmHg) with otherwise normal 24-h systolic and diastolic blood pressures (133/71 mmHg daytime, 119/59 mmHg nighttime).

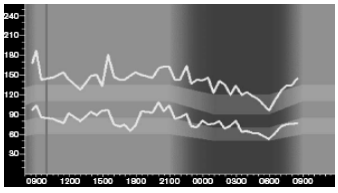


Figure 6: White-coat effect. This ABPM suggests mild daytime systolic hypertension (149 mmHg), borderline daytime diastolic hypertension (87 mmHg), borderline night-time systolic hypertension (121 mmHg) and normal night-time diastolic blood pressures (67 mmHg) with white-coat effect (187/104 mmHg).

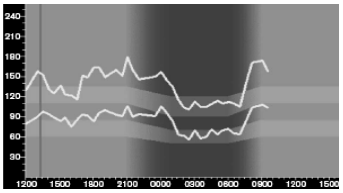


Figure 7: Systolic and Diastolic hypertension. This ABPM suggests mild daytime systolic and diastolic hypertension (147/ 93 mmHg), but normal night-time systolic and diastolic blood pressures (111/66mmHg)

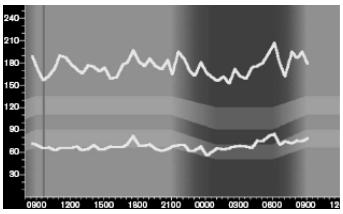


Figure 8: Isolated systolic hypertension. This ABPM suggests severe 24-h isolated systolic hypertension (176/68 mmHg daytime, 169/70 mmHg

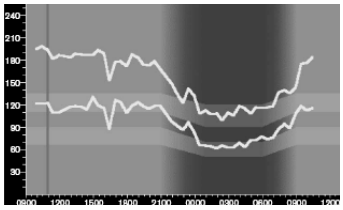


Figure 9: Hypertensive dipper. This ABPM suggests severe daytime systolic hypertension (181 mmHg), moderate daytime diastolic hypertension (117 mmHg) and normal night-time systolic and diastolic blood pressures (111/68 mmHg).

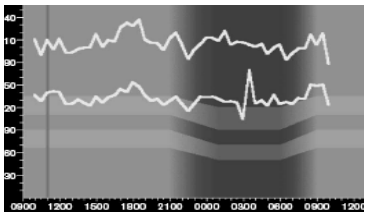


Figure 10: Hypertensive non-dipper. This ABPM suggests severe 24-h systolic and diastolic hypertension (210/134 mmHg daytime, 205/130 mmHg night-time).

Recommendations for Ambulatory Blood Pressure Readings

Currently, an average daytime ABPM of less than 135 mmHg systolic and 85 mmHg diastolic is generally considered normal, but even lower values are being advocated particularly in high-risk groups, such as diabetic patients, in whom values less than 130/80 mmHg are considered optimal.[94]

A prospective study from Japan has demonstrated that ABPM has a prognostic value, and that reference levels can be derived from long-term cardiovascular mortality[114].

The evidence coming from cross-sectional and current longitudinal studies supports lower levels of normality for ABPM, although the levels to be targeted by treatment remain to be established.

Table 4: Recommended levels of normality for ambulatory blood pressure measurements in adults[94]

	OPTIMAL	NORMAL	ABNORMAL
AWAKE	<130/80	<135/85	>140/90
ASLEEP	<115/65	<120/70	>125/65

Table 5: ***Ranges for definitions used in the Ambulatory Blood Pressure Monitoring***[94]

	HYPERTENSION					
	Low	**Normal**	**Borderline**	**Mild**	**Moderate**	**Severe**
Day Time						
SBP	<100	100-135	136-140	141-155	156-170	>170
DBP	<65	65-85	86-90	91-100	101-110	>110
Night Time						
SBP	<90	91-120	121-125	126-135	136-150	>150
DBP	<50	51-70	71-75	76-85	86-100	>100

Ambulatory BP values are usually lower than clinic readings. Awake hypertensive individuals have an average BP of 135/85 mm Hg and during sleep, 120/75 mm Hg. The level of BP measurement using ABPM correlates better than office measurements with target organ injury. ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP fall during sleep. In most people, BP drops by 10 to 20% during the night; those in whom such reductions are not present appear to be at increased risk for cardiovascular events. In addition, it was reported

recently that ABPM patients whose 24-hour BP exceeded 135/85 mm Hg were nearly twice as likely to have a cardiovascular event as those with 24-hour mean BPs less than 135/85 mm Hg, irrespective of the level of the office BP.[10]

Ambulatory Blood Pressure Monitoring in Renal Transplantation.

The prevalence of arterial hypertension in renal transplantation is approximately 60-80% and is usually associated with left ventricular hypertrophy the pathogenesis being multifactorial. Although renal function can improve with renal transplantation there is a component of some degree of renal failure, and immunosuppressive therapy that can exacerbate hypertension along with other risk factors as mentioned above. Studies have been published which state that the ABPM is far more superior than the casual BP in its relation to the graft function and its survival[115]. A rigorous BP control by ABPM appears to be mandatory for the graft survival. Similar to patients on dialysis the non-dipper status approximately 90% is prevalent in the transplant population. The increase in the ambulatory blood pressure during the nocturnal period has been related to the target organ damage and with greater risk of cardiovascular mortality.

In a study of 241 patients on the diurnal variation of blood pressure by ABPM done by Hayadar et.al showed that there were four correlates of SBP diurnal variation (the ratio of the asleep to awake SBP). These were age, renal function (creatinine and GFR), cyclosporine level, and the ABPM-TX(ABPM and Transplant interval time). The first three parameters had a direct relation with diurnal BP, but ABPM-TX had an inverse relationship (i.e., the diurnal variation improved as the time from transplantation

increased). However, correcting for the confounding effect of each risk factor on the other it showed that cyclosporine level and ABPM-TX interval were dependent on the presence of one another or did not affect diurnal variation. Only age and GFR were the truly independent predictors of diurnal BP variation.[116]

The rates of concordance and discordance between casual BP and ABPM-derived BP were 80.6% and 19.4%, respectively[116], as opposed to 63% concordance in a study of 27 renal transplant pediatric patients[117]. In addition, 21% of patients had isolated sleep-related hypertension that was not screened using office or ambulatory daytime BP.[116]

It was concluded by Hayadar et.al that reliance solely on office BP would result in failure to diagnose hypertension in 15% of renal transplant patients. This is why ABPM is a valuable adjunct in the management of post renal transplant cardiovascular risk assessment and treatment.[116]

Gatzka et al. in 1995, who followed 45 renal transplant patients and showed that as time elapsed from transplantation, the diurnal BP variation increased (returned toward normal) regardless of the immunosuppressive agents used [62]. This was contradictory to the subsequent studies that followed by Hayadar et.al[116] and Kooman et.al[118] who concluded that the only independent predictors of diurnal variation of blood pressure were age and GFR.

A prospective study to demonstrate the prognostic superior value of 24-hr ambulatory blood pressure over casual blood pressure in patients after kidney transplantation indicated that 24-hr ambulatory blood pressure profiles, serum creatinine levels, and the

age of kidney donor are strong determinants of graft function after transplantation. When patients were divided into three similarly large groups according to their 24-hr mean arterial blood pressure, those in the upper tertile with a mean arterial pressure ≥97 mmHg had higher serum creatinine levels at 6 and 18 months after renal transplantation. Control of confounding cofactors that are known to potentially influence renal function in transplant recipients such as HLA mismatch, cold and warm ischemic time, organ size, immunosuppressive therapy, CMV constellation, and other cardiovascular risk factors did not differ between groups of tertiles. However, patients in the upper tertile with the highest serum creatinine levels were recipients of grafts from older donors.[115]

On long term follow up it was noticed casual blood pressure was not related to graft function after transplantation, leading to the conclusion that ambulatory blood pressure confers a more precise prognostic marker for graft survival than casual blood pressure measurements. Patients in the upper tertile of mean 24-hr ambulatory blood pressure had a higher rate of renal graft failure than those with a lower 24-hr ambulatory blood pressure.[115]

The link of chronic kidney graft failure with recipient blood pressure has been impressively demonstrated in the Collaborative Transplant Study. The greater the blood pressure post transplantation the less favorable was the long-term kidney graft outcome in the study cohort of 29,751 patients[119]. Arterial hypertension presents a major risk factor for renal allograft survival. However, in all these studies only casual blood pressure was measured which is not as closely related to the degree of target organ damage as 24-hr ambulatory blood pressure readings[120-124].

A prospective study of 1700 Danish men and women, aged 41 to 72 years, without major cardiovascular diseases showed that ambulatory BP provided prognostic information about cardiovascular disease better than office BP. Isolated office hypertension was not a risk factor and isolated ambulatory hypertension tended to be associated with increased risk of target organ damage. A blunted BP decrease at night was a risk factor in subjects with daytime ambulatory hypertension.[127]

Office BP measurements may offer only a spot quantification of the BP load in a given individual. Their reliability may increase with repeated measurements, a practice that should be reinforced among physicians. Even in cases of repeated assessment, however, office BP measurements are unlikely to provide an assessment of BP behavior in daily life, an assessment which can be obtained by out-of-office BP monitoring through either monitoring BP at home or 24-h ABPM.

These observations indeed carry a number of important clinical implications.

(1) A significant proportion of untreated and treated hypertensives, apparently not controlled in the office, are actually controlled out of the office and their cardiovascular risk assessment based only on office BP largely overestimates their real risk.

(2) A significant proportion of untreated and treated hypertensive patients, apparently well controlled in the office, are actually uncontrolled out of the office and their cardiovascular risk assessment based exclusively on office BP largely underestimates their real risk.[95]

Prakash et.al concluded form a study of CKD patients including transplant recipients and hemodialysis patients that in spite of adequate BP control as validated by clinic BP recordings, majority of transplant patients (78.9%) did not have restoration of nocturnal dipping. With regard to BP control the DBP and SBP evaluation at 1 month, there was no difference in daytime and nighttime SBP and DBP in both survivors and non-survivors. However, at 6 months the non-survivors had significantly raised daytime and nighttime DBP and SBP. This was an important predictor of mortality in their group of patients. This persistently raised BP load, was an important predictor of mortality. They also found that a significant higher SBP, attenuation of nocturnal dipping, more LVH (left ventricular hypertrophy) and left ventricular mass index (LVMI) in the non-survivors as compared to survivors. Not withstanding the fact that anemia is strong predictor of LVH and other cardiac complications; an elevated SBP was more important in the causation of LVH and adversely affecting the survival of patients. In their study, nocturnal non-dipping was associated with increased mortality as 80% of non-survivors were non-dippers. Conversely, 55% of the survivors were non-dippers and 45% were dippers.[128]

Verdecchia et.al confirmed that ambulatory BP is more closely related to LV muscle mass than is casual BP. The most important finding, however, of this study was the inverse relation between nocturnal BP decline and LV muscle mass in a large population of unselected and untreated patients with essential hypertension. Only nighttime ambulatory BP disclosed a very evident differentiation between the two hypertensive groups. The findings of this study support the concept that the duration of exposure to increased levels of BP and wall stress over the 24 hours can play an important role in the

pathogenesis of LVH in unselected patients with arterial hypertension. In these patients, a nocturnal reduction of systolic and diastolic BP by more than 10% of daytime values can exert the beneficial effect of delaying or preventing development of cardiac LVH.[130]

In the study by Devereux et al[131], the correlation coefficients between casual or ambulatory BP and LV mass index were generally lower, and in that by Drayer et al [132], generally higher. Both in the study by Devereux et al and in that by Drayer et al, daytime BP showed a generally closer relation to LV mass than did nighttime BP.

In the study by Rowlands et al, [133] awake BP and sleep BP correlated equally well with LV mass, whereas in another study performed on a mixed population of hypertensive and normotensive patients, sleep BP showed a closer relation to LV mass than did awake BP.

Correction of the uremic state by renal transplantation leads to complete resolution of systolic dysfunction, regression of LVH, and improvement of left ventricular dilatation. In fact the reduction of LVH was dependent on adequate renal function and on a decrease in the systolic pressure levels not with diastolic blood pressure levels. LVH reduction was dependent on adequate renal graft function and systolic pressure levels registered by ABPM after transplantation. Renal transplantation had a beneficial impact on the uremic patient's cardiomyopathy, whether it manifested as LVH, left ventricular dilatation, or systolic dysfunction. ABPM detected a high prevalence of persistent hypertension and non-dippers in these patients and was a strong predictor of LVH.[134]

Cuspidi et.al in a study of 611 patients concluded; firstly the classification of isolated clinical hypertension based on a single ABPM reading has limited short term reproducibility. Secondly, repeated ABPM measurements should be recommended to correctly diagnose patients with isolated clinical hypertension and improve cardiovascular risk stratification.[136]

Jokinitty et.al, in his prospective study to evaluate the predictors of LVM and change of LVM of a period of ten years concluded that ambulatory blood pressure improved the prediction of LVM than office blood pressure measurement. Secondly, the pulse pressure was the most significant blood pressure parameter in predicting the future LVMI and change in LVMI.[138-140]

Mean arterial blood pressure after renal transplantation had no significant impact on risk of cardiovascular disease (and patient death). Pulse pressure, as marker for vascular stiffness, was a risk factor for both cardiovascular events and mortality in renal transplant patients, as already has been demonstrated in the general and renal transplant population.[139, 140]

Therefore, the available data do not allow drawing definite conclusions about the possible predominance of daytime or nighttime BP on LVH development in hypertensive patients. **A constant finding in these studies; is the generally closer relation of systolic over diastolic BP to the degree of hypertrophy, another evidence that wall stress, which is mostly related to systolic BP, is a key factor influencing LVH development.**

A personal history of cardiovascular disease before transplantation is a strong risk factor for cardiovascular events after transplantation. The duration of renal replacement therapy before transplantation had an important negative impact on cardiovascular events in our experience, corroborating the advantages of preemptive transplantation.[140]

The intake of steroids was one of the most significant detrimental factors. In this study, most of the patients without steroids either stopped corticosteroids 1 year after transplantation because they had a low immunological risk or entered randomized trials that evaluated the impact of avoiding corticosteroids[143]. Steroid-free patients showed a significant reduced risk of dying or developing cardiovascular events than patients continuing steroids.

The development of de novo diabetes mellitus also was shown to have a strong negative impact on cardiovascular events (and patient survival), reinforcing available data[144]. The importance of renal dysfunction and risk of death and cardiovascular events has recently been stressed in the general population and after myocardial infarction [145,146].

After renal transplantation, serum creatinine at 1 year or at baseline has been shown to be a strong risk factor for cardiovascular death.[147]

Direct, independent association of cardiovascular risk with observed ambulatory blood pressure (BP) and inverse association with the degree of BP reduction from day to night have been established. Daytime and nighttime mean BP, the difference between daytime mean and nighttime mean BP, 24-hour mean pulse pressure, and early-morning BP surge derived from ambulatory blood pressure monitoring (ABPM) data allow the identification of high-risk patients. Although ABPM should not be routinely used for the diagnosis of

hypertension, its use to identify white coat hypertension is particularly appropriate to avoid unnecessary use of antihypertensive therapy.

Data generated by ABPM have established that, even after adjustment for established risk factors, there is a progressive increase in the risk of cardiovascular morbidity and mortality with elevated 24-hour, daytime, and nighttime BP. Also, studies in older Japanese subjects have shown the importance of the early-morning BP surge on target organ damage. The technique of ambulatory BP measurements has become widely adopted to identify effective therapeutic options that provide BP control throughout the dosing interval. Emphasis in the future may focus on the ability of drugs to control the morning BP surge, thereby helping to optimize the control of cardiovascular disease.

In the primary care setting, the contribution of ABPM to the management of hypertensive patients is increasingly acknowledged. Whereas in the past, this technology was considered "experimental," this has changed recently with improved insurance coverage for performing ABPM in specific patients and support for its use in certain subgroups of hypertensive patients by both the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[10] and by the Council on High Blood Pressure Research of the American Heart Association.[153]

AIM

1. To study the role of ambulatory blood pressure monitoring in the renal transplant population.
2. To study the correlation of office, and ambulatory blood pressure monitoring in the live related renal transplant population.
3. To study the correlation of the various methods of blood pressure monitoring with the graft outcome and target organ damage.

PATIENTS AND METHODS

STUDY DESIGN AND LOCATION: This prospective study was conducted at the department of Nephrology, Christian Medical College, Vellore. Patients who underwent renal transplantation from March 2007 to February 2008 were followed up to January 2009.

INCLUSION CRITERIA

- Renal allograft recipients.
- Completed 9 months of follow up.
- Male or female subjects ≥18 years

EXCLUSION CRITERIA

- Pediatric transplantations are avoided as they have different cutoffs for BP control based on the age group.
- Incomplete follow up
- Graft Failure with return to dialysis during the study period.
- Patient death prior during the study period.

METHODOLOGY

PATIENTS: 50 consecutive Renal Allograft recipients who underwent renal transplantation, satisfied the inclusion and exclusion criteria were followed up for 9-12months. Pre-transplant, five patients had a pre-emptive transplant, 44patients were on hemodialysis and one patient was on continues ambulatory peritoneal dialysis. 27patients

received simulect induction 6 patients received anti-thymocyte induction and 17 patients received no induction. 49 patients received immunosuppresion of Prednisolone, Tacrolimus and Mycophenolate Mofetil and one patient received Cyclosporine, Prednisolone and Mycophenolate Mofetil in view of a positive hepatitis C serology.

STUDY DESIGN: Baseline evaluation was performed prior to transplantation. Study procedures included measurement of casual and 24-hr ambulatory blood pressure, a routine laboratory work-up, ultrasound of renal allograft, and a two-dimensional guided M-mode echocardiography was done. Further visits throughout the 9months follow-up period were performed at 2nd, 4th, 6th and 9th month of transplantation and included laboratory tests, casual blood pressure measurements, ambulatory blood pressure measurement and an echocardiography at 9th month.

BLOOD PRESSURE MEASUREMENTS

Office Blood Pressure Measurement Protocol

A total of three office blood pressure measurement was taken by a trained doctor according to the suggestions of the World Health Organization (WHO). Blood pressure measurements were performed with a standard sphygmomanometer in a sitting position after 10 min of rest with cuff size adjusted according to the individual‘s arm circumference. Timed measurements of casual blood pressure were taken during the initiation and termination of the ambulatory blood pressure measurement.

Ambulatory Blood Pressure Monitoring Protocol. Blood pressure was recorded non-invasively with a commercially available device Welch Allyn ABPM 6100 Ambulatory Blood Pressure Monitor over 24 hr on a regular working day. Each recording started at 9am and ended 9am the next day. 24hr-readings were taken at an interval of half hour during the day and night. The patients were asked to maintain a diary to document the time the went to asleep and awoke. Blood pressures were obtained in the non-dominant arm however in the presence of an arteriovenous fistula the cuff was applied on the other arm. Ambulatory blood pressure values given in the tables reflect the timed measurement of blood pressure with the office blood pressure. From the blood pressure monitors data, mean BP while awake, mean BP during sleep and mean 24 hr BP and pulse rates were derived. ABPM derived BP levels were reported to normal standards, derived from large populational studies.

ABPM hypertension was defined as following: daytime BP>135/85; nighttime BP > 120/75; 24hrs. BP>130/80 [155]. Normal circadian rhythm was defined as a sleep-to awake BP ratio>0.92 (systolic BP) and >0.90 (diastolic BP); these values were taken from a normal population from the study of Staessen et al.[156] Patients were classified as Dipper: 0.8-0.9, Non-dipper: 0.9-<1, Inverted dipper: >1 [155-156] SBP diurnal variation was defined as average asleep-awake SBP. A high morning surge was defined if more than >20% of the mean a 24hr ABPM were ≥ 135/85. Casual hypertension was defined as office BP greater than 140/90 mm Hg.[25] Hypertension by ABPM was defined on the basis of average daytime measurements of SBP greater than 135 mm Hg and diastolic BP (DBP) greater than 85 mm Hg; or nighttime SBP greater than 125, DBP greater than 75 mm Hg,

or both.[94] The protocol was approved by the Clinical Investigation Ethics Committee and Institutional review board of the institution.

Echocardiography: It was performed with commercially available Philips equipment (model: iE 33), with a 2.5-mHz mechanical transducer.

The following structural parameters were evaluated: interventricular septal thickness in systole; interventricular septal thickness in diastole; left ventricular end systolic diameter (LVESD); left ventricular end diastolic diameter (LVEDD); left ventricular posterior wall thickness in systole; left ventricular posterior wall thickness in diastole; LVM; left ventricular mass index and (LVMI) estimated by the ratio between the LVM and body surface area.

The LVM was calculated by the modified formula of the American Society of Echocardiography: [131,158,159]

LVM= 0.80{1.04(LVEDD +ISTD+LVPWTD)3-(LVEDD)3}+0.6

LVH was defined as a LVMI value greater than 134 and 110 g/m^2 for men and women.[160] The percentage variation (Δ) of the LVMI before and 12 months after transplantation was also calculated:

Delta (Δ) = LVMI pre-transplant-LVMI post transplantation/ LVMI pre-transplantation*100 [158,159]

Laboratory work-up: All renal transplant recipients underwent a routine laboratory work-up at least every point of the visit after kidney transplantation which included urine

analysis, serum creatinine, serum urea, serum uric acid, serum electrolytes, Cyclosporine levels, Tacrolimus and Mycophenolate levels, and complete blood cell count. eGFR was calculated using the abbreviated MDRD formula.

Statistics: Descriptive statistics was used to describe the demography, clinical, laboratory characteristics, office and ABPM registries. A repeated measure of ANOVA, logistic regression and paired't' test was used for the comparison of the various variables accordingly.

Bland Altman plot was plotted over time for CABP (2^{nd}, 4^{th}, 6^{th} month post transplant) against mean difference of office-CABP for both SBP and DBP. Error bars with 95% confidence interval was plotted over time for SBP and DBP against the number of dugs and over time. The following risk factors were considered for the GEE analyses: weight, BMI, casual BP, laboratory variables, ABPM registries, and office BP to identify predictors for good control of blood pressure.

All analyses were performed using a SPSS 16.0 and SAS 9.1 and STATA 10.0 Statistical methods included: linear regression, repeated measure Chi-square, t-testing, all with two-tailed significance. However, the Blood Pressures measured over time (baseline, 2, 4, 6 months) were analyzed using Generalized Estimating Equations (GEE) method, where the individual level correlations (repeated measures) were identified using Quasi Information Criteria (QIC) and the correlation structure was adjusted in the analyses. The Statistical Analyses System (SAS) 9.1 software was used to do the above method.

Results

Patient Profile:

Consecutive patients who had adult renal transplantation between March 2007 to February 2008 and completed 9months of follow up by January 2009 were enrolled in the study.

Figure 11. Patient Profile of the Study

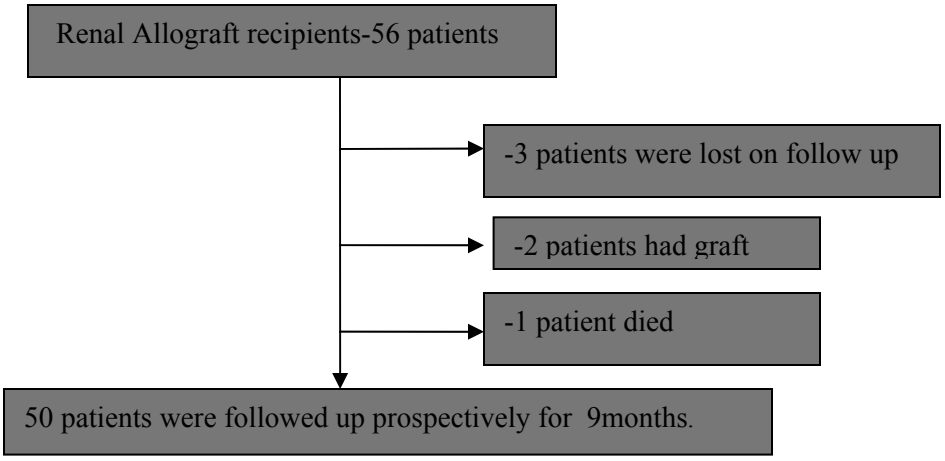
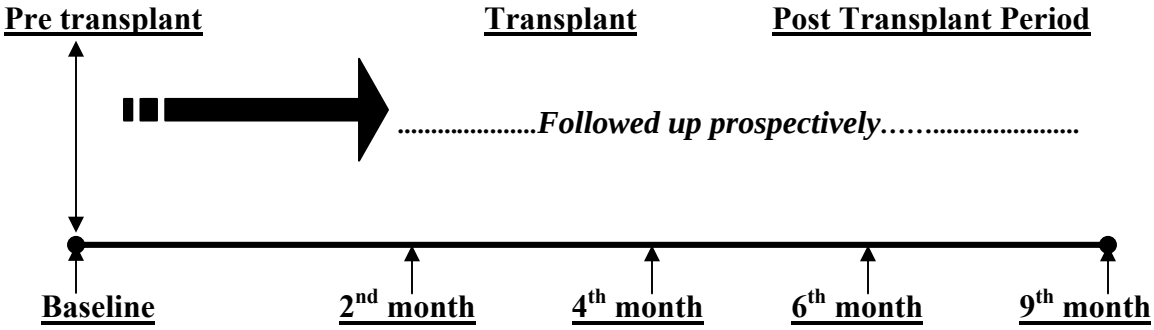


Figure 12: Clinical Course During the Study



CABP, Office BP	CABP, Office BP, Laboratory and Clinical Assessment.
Laboratory, Clinical	Echocardiography at 9th month.
ABPM Diary, Echocardiography	

Demography Profile: This study comprised of 50 patients who underwent live related renal transplantation (Table 6); of which 40 patients were male recipients and 29 were female donors. Pre-transplant hypertension was 94% which had reduced to 72% post transplantation. The majority of the patients (86%) were on either two or more than two drugs while 14% were not on anti-hypertensives in the pre-transplantation period. In the post transplantation period 72% of the patient's required anti-hypertensive medication and 28% of them required no anti-hypertensive drugs. Mean duration of dialysis was 6±6 months (median: 3.5months, Range: 0-28months) pre-transplant.

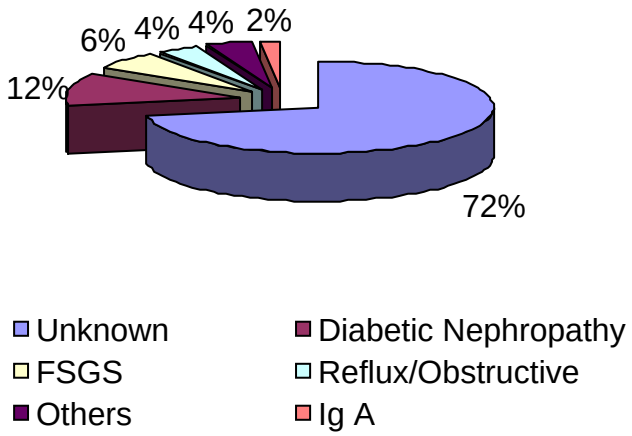
Table 6 Demography Profile; n=50; *Mean ± SD, ** (Min-Max), ***n (%)

Males: Females (Recipients)	40:10 (4:1)
Males: Females (Donor)	21:29 (1: 1.3)
**Donor's Age(years),	40± 11.6
**Recipient's Age(years)	35± 11
***Pre-Transplant DM	6 (12)
***Post Transplant DM	11 (22)
***Pre-Tx Hypertension	47 (94)
***Post Tx Hypertension	36 (72)
***Anti-HTN Drug Pre-Tx	Nil:7 (14), ≤ 2drugs:30 (60), >2drugs: 13 (26)
***Anti-HTN Drug Post-Tx	Nil:14 (28), ≤ 2drugs:23 (46), >2drugs: 13 (26)
*Duration of Dialysis in months	6 ± 6
***HLA	<2 Ag Match: 16 (32), ≥2 Ag Match: 34 (68)

***Induction	Yes: 33(66), No: 17(34)
*Warm Ischemic Time (min)	5.3 ± 6.6
*Cold Ischemic Time (min)	70.2 ± 20.6

Native Kidney Disease: 72% of the patient's native kidney disease was unknown and 12% were diabetic nephropathy while 16% of them had other glomerular nephritis.

Figure 13: Native Kidney Disease



Immunosuppression : 65% of the patients received induction either ATG of IL2 prior to transplant. 90% of the patients received primary immunosuppresion as Prednisolone (Pred) +Tacrolimus (Tac) and Mycophenolate (MMF) while 2% of the patients received Pred+Tac and Azathioprine. One patient was serology positive for hepatits C and hence was on cyclosporine as part of his immunosuppressive protocol. A significant increase in the cumulative dose of steroids and Tacrolimus were noted over the post transplantation period.

Table 7 Immunosuppression

Immunosuppresion	n (%)
Pred+Tac+MMF	45 (90)
Pred+Tac+Aza	4 (8)
Pred+CsA+Aza	1 (2)

Immunosuppresion	2nd Month	4th Month	6th Month	9th Month
Tacrolimus in ng/ml	328.3±89.4	619.7±171	890.6±274.9	1269.9±435.9
Steroid &Methyl Pred (mg)	1096.8±508.9	1760.2±524	2134.5±260.2	2951.6±357.2

Laboratory and Clinical Charateristics

76% of the patients had no rejection, 24% had acute rejections of which 8% had one rejection episode, 12% had two rejection episodes and 4% had three rejection episodes. In these rejection episodes 11 episodes were acute cellular rejection (reversible with steroids) and two episodes were acute vascular rejection (steroid resistant but reversible with ATG). In the immediate transplant there was an increase in the BMI which remained stable in the remaining period of follow up. The office BP and the ABPM registries, renal function, albumin, 24hr proteinuria improved during the post transplantation period as represented. The office SBP and DBP, mean SBP and DBP, Awake SBP and DBP, Asleep SBP and DBP, Awake-Asleep SBP and DBP and MAP did not have any significant correlation with eGFR and creatinine at all time points.

Table 8. Laboratory Characteristics, n=50

Characteristics	Pre-TX	2nd Month	4th Month	6th month	9th month	p value
Creatinine	4.7±1.4	1.1±0.2	1.2±0.2	1.2±0.2	1.2±0.2	0.0
eGFR	15.9±5.1	75.6±17	71.6±18.7	71±17.3	69.5±16.7	0.0
Albumin	3.6±0.5	4.3±0.3	4.4±0.4	4.4±0.4	4.5±0.2	0.0
24hr Proteinuria	2338.5±2093.3	316.3±612	316.5±854.3	249±440	200.6±171	0.0

Table 9: Clinical Profile

Characteristics		Pre-Tx	2nd Month	4th Month	6th Month	9th Month	p value
BMI		20.6±3.6	21.0±3	21.9±3.1	22.4±3	22.9±3.7	0.0
Office BP	**SBP**	140±16.1	120.3±9.7	120.1±11.3	120.7±9.2	120.1±9.4	0.0
	DBP	88.2±8.9	82.1±7.6	78.7±7.6	78.7±7.2	79.4±6.7	0.0

Table 10: ABPM Pre-Tx, 2nd, 4th, 6th, 9th month after transplantation, m ean±SD

BP Readings	Pre-Tx	2nd	4th	6th	9th	p value
SBP	127.2±14.7	120±9.6	117.9±7.9	118.7±7.4	117.2±8.3	0.0
SBP Awake	127.7±14.9	119.8±94	118.9±7.7	118.9±7.3	118.1±8.9	0.0
SBP Asleep	124.6±16.3	120.3±11	117.6±9.6	117.8±8.4	116.9±9.3	0.0
DBP	81.2±13.6	73.1±7.4	71.9±6.8	72.2±5.9	71.0±6.7	0.0
DBP Awake	80.9±11.7	73.5±7.5	72.2±6.9	72.8±5.9	72.0±7.8	0.0
DBP Asleep	77.2±12.3	72.5±8.2	70.9±7.6	71.4±7.1	69.9±7.0	0.0
Awake-Asleep SBP	0.98±0.08	1.0±0.07	1.0±0.07	1.0±0.07	0.9±0.07	0.0
MAP	65.5±13.6	57.5±8	56.5±7.9	56.8±6.8	55.6±7.5	0.0
Awake-Asleep DBP	0.95±0.09	0.98±0.0	0.98±0.08	0.99±0.07	0.97±0.08	0.0

Office and ABPM Before and After Renal Transplantation

Concordance or Discordance between Office BP and ABPM-Derived BP

Equivalence study (Table 10) for the comparison of times matched measurements for office and ABPM showed the upper confidence interval of 5-7units the maximum. At each time point the office measurement tend to overestimate the blood pressure by 22-70% for SBP and DBP.

Table 11: Comparison of Office and ABPM BP Measurements; Mean±SE

Time	Office	CABP	95% CI	t-value
Systolic BP				
Month 2:	121.18± 1.55	121.52±2.1	-5.38 to 4.69	1.42
Month 4:	122.02±1.45	119.27±1.71	-1.62 to 7.12	3.03
Month 6:	121.09±1.35	117.96±1.22	-0.69 to 6.95	3.65
Diastolic BP				
Month 2:	80.9±1.09	76.75±1.51	0.56 to 7.74	4.45
Month 4:	81.18±0.79	76.16±1.29	2.16 to 7.88	6.18
Month 6:	79.88±0.80	72.82±1.06	3.96 to 10.15	7.01
Mean Arterial Pressure				
Month 2:	67.47±1.15	61.83±163	1.79 to 9.48	4.92
Month 4:	67.57±1.01	61.79±1.38	2.49 to 9.07	5.83
Month 6:	66.14±0.80	57.77±1.25	4.79 to 11.95	6.78

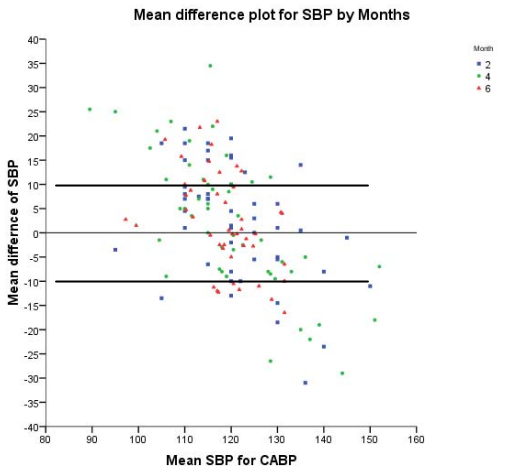
Table 12: Risk factors for SBP and DBP

A GEE analysis for the risk factors showed no significant predictors for the control of SBP, DBP and MAP.

Risk Factors	SBP, p value	DBP, p value	MAP, p value
HLA	0.4	0.2	0.5
Recipient Age	0.1	0.1	0.1
Donor's Age	0.6	0.5	0.6
Rejection Episodes	0.6	0.9	0.5
Recipient's BM	0.4	0.2	0.4
Proteinuria	0.3	0.7	0.7
Creatinine	0.5	0.9	0.3
WIT	0.7	0.3	0.9
CIT	0.3	0.8	0.1
Duration of Dialysis	0.6	0.8	0.4
Donor's DTP	0.8	0.7	0.6
Donor's Mean SBP	0.4	0.5	0.3
Donor's Mean DBP	0.2	0.3	0.2
Baseline SBP of Recipient	0.4	0.2	0.07
Baseline DBP of Recipient	0.2	0.3	0.06

A Bland Altman plot (Figure 13) for similarity showed the tendency for the office to blood pressure to be overestimated when the ABPM readings were low and underestimate when the ABPM readings were high for SBP and DBP.

Figure 14: Bland Altman Plot comparing the SBP, MAP and DBP of ABPM with Office BP Measurement



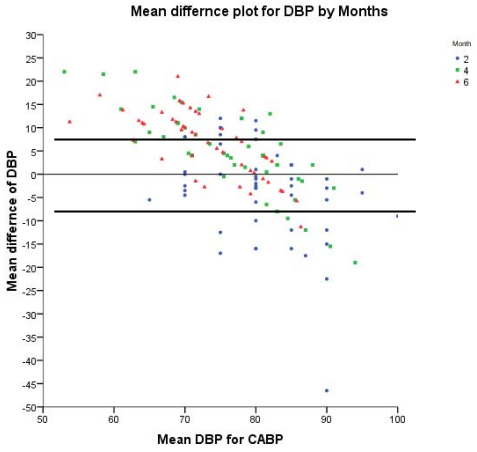
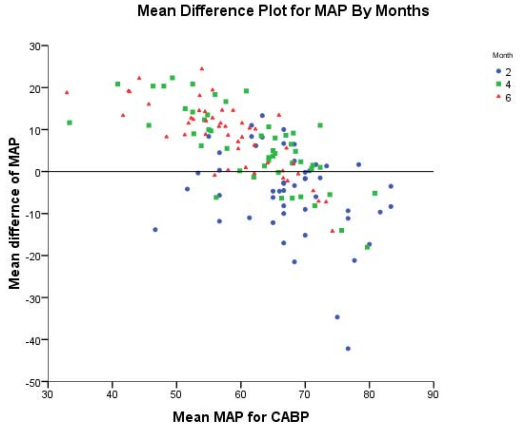
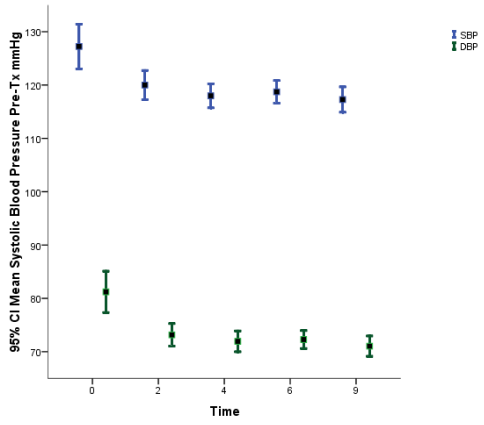


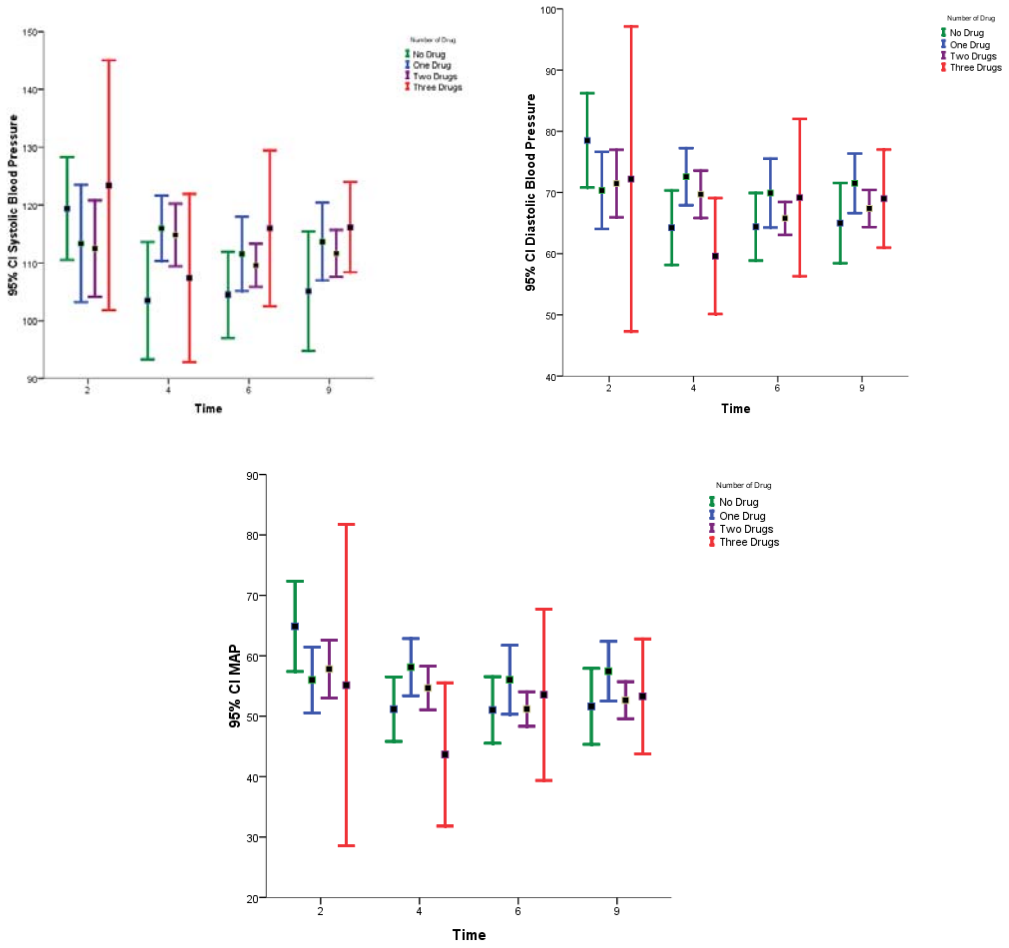
Figure 15: SBP and DBPM of ABPM over time





However the blood pressure control improved over irrespective of time and the number of drugs used at each time point. (Figure 14, 15)

Figure 16: Relationship of SBP,DBP and MAP irrespective of drugs and Duration of Transplant



Circadian Abnormalities Before and After Renal Transplantation

Pre-Transplant 15(30%) patients were dippers, 29 (58%) patients were non-dippers and 6 (12%) patients were inverted dippers. During the follow up period there was an initial decline of dippers to 16% at the 2nd month subsequently the dippers increased to 20% at

4th month, 24% at 6th month to 28% at the 9th month. However there was an increase in the non-dippers to 72% at the 2nd month followed by a gradual decline to 66% in the fourth and sixth month to 60% at ninth month. The inverted dippers fluctuated between 12%-14% from pre-transplant to their last follow up at the 9th month.

A sub-analysis (Table 13) of these three groups of patients showed among the true dippers at pre-transplant only six patients (40%) continued to be dippers at the 9th month while another six patients (40%) had become non-dippers and three patients (20%) became inverted dippers. Among the true dippers only one patient maintained its dipping status throughout the follow up period. Among the true non-dippers at pre-transplant twenty patients (68%) continued to be non-dippers, seven patients (24%) had become dippers and two patients (8%) had become inverted dippers at 9th month after renal transplantation. Among the true inverted dippers four patients (66%) had become non-dipper, one patient (16.6%) had become dipper and one patient (16.6%) continued to be an inverted dipper at the 9th month post transplant.

Despite a successful renal transplantation and a good control of blood pressure, 68% of the patients maintained their non-dipping profile as 40% of them had a persistent high morning surge at 9th month post renal transplantation.

Table 13.Dipper vs Non-Dipper vs Inverted Dipper Before and After Tx ;n(%)

Characteristics	PreTransplant	2nd month	4th month	6th month	9th month
Dipper	15 (30)	8 (16)	10 (20)	12 (24)	14 (28)
Non-Dipper	29 (58)	36 (72)	33 (66)	33 (66)	30 (60)
Inverted Dipper	6 (12)	6 (12)	7 (14)	5 (10)	6 (12)

78% had the normal circadian rhythm and 22% had an abnormal circadian rhythm of their blood pressure at pre-transplant. During the post transplantation period at various time points there was mild improvement in the normal circadian rhythm for blood pressure with 84% at 9th month.

Table 14. Circadian Rhythm Profile; n=50, n(%)

Characteristics	Pre TX	2nd month	4th month	6th month	9thmonth
Normal Circadian Rhythm	39 (78)	47 (94)	45 (90)	47 (94)	42 (84)
Abnormal Rhythm	11 (22)	3 (6)	5 (10)	3 (6)	8 (16)

Though there was improvement in the circadian rhythm profile (Table 14,15) of the patients, the non-dipping profile from 71.8% at pre-transplant reduced to 69% at 9th month of post transplantation. Among the non-dippers who had no improvement of their circadian rhythm 40% of them had a persistent high morning surge of their blood pressure at 9th month. Most importantly, the dipping profile in this cohort had improved from 12.8% at pre-transplant to 16.8% post transplant. This would be due to the reduction of morning surge in 25% of pre-transplant true dippers to 21% at 9th month of post transplantation. Isolated nocturnal hypertension was present in 16(32%) of the patients pre-transplant which reduced to significantly during the follow up to 7(14%) patients at 2nd month, 4(8%) at 4th month, to 2(4%) by the 6th and 9th month post transplant. In this group the true non-dippers 12(41.4%) who had nocturnal hypertension at pre-transplant made a significant improvement over the period time with the incidence reducing to 3.3% at 9th month of post transplant

Table 15.Circadian Rhythm and Dipper Profile n= 50, n(%)

Circadian Rhythm	Pre-transplant			9th month Post Transplantation		
	Dipper	Non Dipper	Inverted Dipper	Dipper	Non Dipper	Inverted Dipper
Normal	5 (12.8)	28 (71.8)	6 (15.4)	7 (16.7)	29 (69)	6 (14.3)
Abnormal	10(90.9)	1 (9.1)	-	7 (87.5)	1 (12.5)	-

Predictors of Circadian Rhythm Abnormalities

In those patients with an improved diurnal BP rhythm with a non-dipping profile an univariate linear regression analysis (Table 16 & 17) with the following risk factors: recipient age, duration of dialysis, pre-transplant and post transplant diabetes and hypertension, eGFR, creatinine, recipient BMI, mean SBP, DBP, Awake SBP and DBP, Asleep SBP and DBP showed mean SBP and DBP, Awake SBP and DBP at 9th month of post renal transplantation were significant ($p \leq 0.05$). However a multivariate regression analysis showed none of these risk factors were independent predictors to normal circadian rhythm of blood pressure.

Table 16. Univariate Analysis

Pre transplant		Post transplant	
Risk factors	p	Risk Factors	p
Recipient Age	0.9	Recipient Age	0.4
Recipient BMI	0.1	Recipient BMI	0.6
Dialysis Duration	0.7	DM	0.2
DM	0.9	Hypertension	0.7
Hypertension	0.7	**Mean SBP**	**0.04**
Mean SBP	0.08	**Mean DBP**	**0.02**
Mean DBP	0.1	Creatinine	0.9
Creatinine	0.6	eGFR	0.8
eGFR	0.9	**Awake SBP**	**0.002**
Awake SBP	0.8	**Awake DBP**	**0.004**
Awake DBP	0.06	Asleep SBP	0.8
Asleep SBP	0.4	Asleep DBP	0.8
Asleep DBP	0.8		

Table 17. Multivariate Analysis

Risk factors	p value
Post Tx Mean SBP	0.9
Post Tx Mean DBP	0.9
Post Tx Awake SBP	0.9
Post Tx Awake DBP	0.9

LVH,LVM and LVMI before and after Renal Transplantation

There was significant reduction in LVH from 24 (48%) at pre-transplant to 9(18%) at 9th month of post transplant. On gender basis as per the criteria LVH was noted to be 20(40%) in men and 4(8%) in women which had reduced to 5 (10%) in men and remained the same for the women after renal transplantation. Among the women two

patients who had pre-transplant LVH continued to have LVH and two new patients with LVH pre-transplant had developed LVH. The LVM pre-transplant was 197.2 ± 68.5 which reduced to 167.4±41.2 The LVMI at pre-transplant was 128.3±63.4 and at 9th month of post transplant was 101.2±24.2. There was a reduction of 30% in LVM and 27% reduction in the LVMI at 9th month post transplant.

Table 18. LVH, LVM, LVMI before and after transplantation; mean±SD, n(%)

Characteristics	Pre-TX	Post TX-9th month	p value
LVH	24 (48)	9 (18)	0.05
LVM	197.2±68.5	167.4±41.2	0.01
LVMI	128.3±63.4	101.2±24.2	<0.05
ΔLVMI	9.3±36.0		0.07

Risk Factors for LVM, LVMI and ΔLVMI

To study the influence of recipient age, duration of dialysis pre-transplant, pre-transplant and post transplant diabetes mellitus, hypertension, creatinine and eGFR, no of anti-hypertensive drugs and the 24hr BP levels we analyzed for positive predictors for LVM and LVMI at pre-transplant and 9th month of post renal transplantation. A univariate analysis (Table 19) showed pre-transplant BMI, duration of dialysis, diabetes mellitus, number of anti-hypertensive drugs, creatinine, eGFR, mean DBP and asleep DBP at pre-transplant were significant for LVM. For LVMI except for pre-transplant diabetes mellitus the other risk factors were significant at pre-transplant. At 9th month of post transplant a univariate analysis showed significant correlation for duration of recipient age, BMI, post transplant diabetes and hypertension, creatinine, eGFR duration of dialysis, number of anti-hypertensive drugs, mean DBP and asleep DBP to be significant

for LVM and LVMI. However for ΔLVMI in addition to duration of dialysis pre-transplant, age of the recipient, number of anti-hypertensive drugs at 9th month; 24hr BP registries such as mean SBP and mean awake and asleep SBP were significant.

Table 19.Univariate Analysis for LVM,LVMI before and after transplantation at 9th month; p value

Risk Factor	Pre-Tx LVM	Pre-Tx LVMI	Post Tx LVM	Post Tx LVMI
Recipient Age	0.8	≤0.05	≤0.05	≤0.05
Recipient BMI	≤0.05	≤0.05	≤0.05	≤0.05
Duration of Dialysis	0.2	≤0.05	≤0.05	≤0.05
Pre Tx & Post Tx DM	0.04	0.07	≤0.05	≤0.05
Pre Tx & Post Tx HTN	≤0.05	≤0.05	≤0.05	≤0.05
Anti-Hypertensive drugs	≤0.05	≤0.05	≤0.05	≤0.05
Creat at Pre and Post	≤0.05	≤0.05	≤0.05	≤0.05
eGFR at Pre and Post	≤0.05	≤0.05	≤0.05	≤0.05
Mean SBP	0.02	≤0.05	0.8	0.8
Mean DBP	≤0.05	≤0.05	0.03	0.04
Mean Awake SBP	0.04	≤0.05	0.7	0.6
Mean Awake DBP	0.04	≤0.05	0.06	0.04
Mean Asleep SBP	0.02	≤0.05	0.1	0.3
Mean Asleep DBP	≤0.05	≤0.05	0.02	≤0.05

A multiple linear regression (Table 20) of these significant factors at these two time points showed that duration of dialysis pre-transplant, post transplant hypertension and number of anti-hypertensive drugs at 9th month were positive predictors at the 9th month of post transplantation for LVM and LVMI. No predictors were significant at pre-transplant for LVM and LVMI. At 9th month duration of dialysis pre-transplant was significant for ΔLVMI.

Table 20.Multivariate Analysis of LVH after renal transplantation at 9th month

Risk Factor	LVM	LVMI	ΔLVMI
Duration of Dialysis Pre-Transplant	0.04	0.04	0.04
Post Transplant Hypertension	≤0.05	≤0.05	0.3
No: Antihypertensive Drugs at 9th month	0.03	0.001	0.9

Discussion

Hypertension is a powerful predictor of renal transplant outcome; however, accurately diagnosing high BP remains a challenging task in renal transplant recipients. Several previous studies in renal transplant patients have shown abnormal ABPM hypertension-diurnal rhythm. The incidence and predictors of hypertension-abnormal diurnal BP rhythm in this patient population remain unclear. Majority of the studies have been done on a cyclosporine population and very few data available on a tacrolimus population in adult renal transplantations though data are available in the pediatric renal recipients. What has been lacking to date is a large-scale study of these issues in renal transplant patients in India.

This is a study which has prospectively analyzed the diurnal BP rhythm profiles from dialysis to engraftment, a difference in the categorization of patients as normotensive and hypertensive subjects by the use of ABPM and to see the comparison of office BP with ABPM. In this study we also analyzed the effects of a successful renal transplantation and BP on the morphology of the left ventricle as evaluated by Doppler echocardiography, particularly the influence of various risk factors on the development of LVM, LVMI and ΔLVMI.

Our data demonstrate an over estimation of office blood pressure at all time point when compared to ABPM. The difference range from 4-7mmHg of SBP and DBP of office BP *vs.* ABPM. At each time point the office blood pressure overestimates 22%-70% in our study. A problem with ABPM measurement is that the definitions of "normal," thresholds

for intervention, and targets for treatment are all less well defined than for clinic BP. A review of literature shows the degree for office BP to overestimate ABPM measurements varies in each study undertaken. Authors opine a difference of 4-7mmHg to 10/5mmHg in their respective studies. [115,116,117] Unfortunately, no algorithm or regression equation can be determined from comparative studies, because ABPM is both underestimated and overestimated by CBP measurements.[117,161] Overestimation may be attributable to white-coat hypertension or to a normal nocturnal dipping, whereas underestimation could be explained by the fact that the studied patients take their antihypertensive medication shortly before the CBP morning measurement [117,161] or because they have a high nocturnal BP level. Possibly, more often, mean 24-hr BP levels, as determined by ABPM, exceed CBP levels

This study did not show the presence of any risk factor like recipient's age, duration of dialysis, pre-transplant hypertension and diabetes, HLA mismatches, rejection episodes, cumulative dose of steroids and tacrolimus, induction, pre-transplant BMI, pre-transplant creatinine and GFR, WIT and CIT, baseline SBP and DBP by GEE analysis for the control of blood pressure after taking into the consideration of the confounding factor such as number of anti-hypertensive drugs. This study showed that the blood pressure remained under good control over time irrespective of the number of anti-hypertensive medications showing that number of drugs can predict the severity in controlling the blood pressure but not the variability of the blood pressure in the diurnal rhythm of blood pressure control as shown with a wide variation in the standard error of the mean SBP, DBP and MAP readings in the 24hr ABPM(Figure 13&15). There was also no

significant correlation of ABPM registries in relation to renal function in our study and target organ damage. This could be possible due to the fact that the target organ damage and alteration in renal function can be correlated only in a long term follow up of patients which is a limitation in our study. Unlikely in Jacobi et.al and Covic et.al who showed the baseline creatinine and 24hr SBP and DBP had significant impact on graft failure who were followed up for 5years.[115,161]

Studies in adults describing the immediate impact of successful renal transplantation on the circadian BP profile and BP variability are few. Our study showed a significant improvement of circadian rhythm of blood pressure from 74% to 94% in the immediate post transplant period and subsequently to 84% at 9th month of post renal transplantation. This could be due to three reasons; firstly, the significant reduction in the nocturnal hypertension from 32% to 16% at 2nd month and subsequently to 4% by the 9th month among the pre-transplant non-dippers with nocturnal hypertension (41.4%) to 3% at 9th month. Secondly the use of tacrolimus immunosuppresion than a CsA based regime. Thirdly, probably due to an aggressive control of blood pressure. A univariate analysis showed mean SBP, DBP and awake SBP and DBP were positive predictors for a normal circadian rhythm. None of these factors were significant on multivariate analysis. At the same time, diurnal variation was not influenced by: duration of dialysis, pre-transplant diabetes and hypertension number of rejection episodes or HLA, mismatches, type of antihypertensive medication.

Our result was contradictory to the studies which showed a worsening of circadian rhythm of blood pressure in the immediate transplant period the main reason being that most of the studies done of 24hr ABPM have been assessed on cyclosporine based immunosuppressive regime and ours have been a 94% tacrolimus based immunosuppressive regime. Data on the influence of tacrolimus in renal transplant population on 24hr BP profile are less where the incidence of nocturnal hypertension, non-dipping status, variability in circadian rhythm are less in tacrolimus when compared to CsA.[162] Majority of the studies have been on pediatric and liver transplant recipients. Hence more control studies are required to study the anti-hypertensive effect of CsA and Tacrolimus. A study was performed by Fereira et al. in which 24 patients with ESRD were prospectively studied by ABPM before and at 3, 6, and 12 months after renal transplantation (CsA/Pred/MMF regime). A significant drop in the mean values of daytime and nocturnal systolic blood pressure at 12 months after transplantation was recorded. All patients were non-dippers before transplantation, but only two patients (8.3%) were dippers, 12 months after transplantation. Patients were randomly selected from the center's living related program, but it is not clear if this was not a particular subgroup population, when we take into account the rather unusual 80%-100% nondipping prevalence before transplantation.

A prospective study by Covic et.al where 20 consecutive renal allograft recipients

(CsA/Pred/MMF) were analyzed. This study showed severe worsening of the circadian profile, at 1 month following renal transplant, when all subjects are non-dippers, 80% having in fact higher nocturnal BP compared to diurnal levels which did recover to a normal circadian profile in one third of the initial pre-transplant non-dippers in the late

transplant period. They also showed that in the immediate transplant there were no predictors for circadian variability but late transplant period diurnal variation was only influenced by the age of the recipient and eGFR at post transplant period.[164] Faria et.al and Ligtenberg et.al should a significant initial worsening of circadian rhythm of blood pressure with a tendency towards attaining a normal rhythm over time for patients on CsA when compared to Tacrolimus.[162,165] This could also be a reason in our study to show a low incidence of abnormal circadian variability and nocturnal hypertension in the immediate transplant period as shown in other studies where in predominant immunosuppresion were CsA based regime and load of immunosuppresion is high. Over time as the immunosuppresion is tapered the incidence of non-dipping reduces with an improvement of circadian variability as reported by these same studies on their follow up.[162, 165]

In the study of Gatzka et al., the prevalence of dippers increased from only 27% in the early post transplant phase to 73% in the late phase (>1 year); this effect was independent of the level of mean 24 hr-BP and of the antihypertensive and immunosuppressive medication.[166] Our data showed no significant change in the dipper status. Despite a successful renal transplantation and a good control of blood pressure 68% of the patients maintained their non-dipping profile at all time points and the dipper status improved marginally suggesting the need for a longer duration of follow up and ABPM.

After more than 1 year following transplantation, the major determinants of the circadian variability are the level of the renal function, and the initial dipping profile. Covic et.al

reported 55% at one year post renal transplantation.[161, 164] In our cohort no significant predictors of the circadian variability and non-dipping status were identified. This observation, coupled with the fact that a significant proportion of patients maintain their nondipping profile unchanged, suggest that some changes are irreversible despite successful renal transplantation and a well controlled blood pressure profile during the post renal transplantation period and would require a long term follow up.

LVH is the main feature found in chronic uremia, being present in 75% of patients who begin ESRD therapy. It is considered an independent cardiovascular risk factor, which significantly raises the chance of sudden death, heart failure, coronary artery disease, and cardiac arrhythmias. Our study showed a 30% reduction in LVH with corresponding 30% and 27% reduction in LVM and LVMI. This had a beneficial outcome on LVH Studies in literature show a significant change noticed only after one year post transplantation. The use of CsA based regime as demonstrated by Lipkin et al. in his study of ambulatory blood pressure and left ventricular mass in cyclosporine and non-cyclosporine treated renal allograft recipients found a nondipping pattern more frequently among cyclosporin treated patients and associated with a higher left ventricular mass. The improvement in LVH could be attributed to the use of tacrolimus regime in our population. Association of risk factors (Table 18, 19) with single and multiple regression analysis showed that the duration of dialysis, number of anti-hypertensive drugs post transplant and post transplant hypertension were significant predictors for reduction in LVM and LVMI and duration of dialysis was significant predictor for ΔLVMI. The significance increase number of anti-hypertensive drugs can be an indirect predictor of the severity of post transplant. Our

study did not show any significant BP measures (Office of ABPM) as reported by studies[134,161,164] in literature; probably due to the good control of blood pressure, lowest immunosuppresion with therapeutic drug monitoring at post transplant at all time points of follow up.

The value of ABPM in renal transplant recipients will be adequately appreciated only when a randomised trial is undertaken, with BP therapy decisions based on ABPM versus office BP measurements, in matched cohorts, and with graft survival and major adverse cardiovascular events as hard endpoints.

Conclusions

In renal allograft recipients from India the study concluded that:

1. Office BP measurements (SBP and DBP) tend to record higher when ABPM records lower readings and lower readings are recorded by Office BP when the ABPM readings are higher. The difference being 4-7units of mmHg.
2. Blood pressure was well controlled in the post transplantation period with multiple variable drugs.
3. Office and ABPM measurements did not correlate with renal function in the early post transplant period. A longer duration of follow up is required to see the association of BP measurements in our population.
4. No significant risk factor was associated with the blood pressure variability, diurnal rhythm of BP, and dipping status in our population
5. There was mild improvement of circadian rhythm noted in early transplant period the variability of diurnal rhythm in late transplant period requires a longer duration of follow up.
6. A significant reduction in nocturnal hypertension among the true non-dippers was noticed in this study at early transplant.
7. Duration of dialysis, post transplant hypertension and the number of anti-hypertensive drugs at post transplant are positive predictors in reduction of LVM, LVMI and improvement in ΔLVMI.

Thesis Proforma

Name of Recipient:

Hospital No:

Addresses:

Phone Number: e-mail:

Sex:

1. M 2. F

Age of Recipient: Date of Transplant:

Relationship:

1. Parents
2. Siblings
3. Children
4. Spouse
5. Other: Cousin, Aunt, Uncle, Grand

Donor's Age

1. >20≥30
2. >31≥40
3. >41≥50
4. >51

Donor's Sex:

Female -0 / Male -1

Donor HT: Donor Weight:

Donor DTPA GFR before Transplant:

Pre Tx DM : No – 0 / Yes – 1

Pre TX HTN: No – 0 / Yes – 1

Preemptive TX: No – 0 / Yes – 1

Duration of Dialysis in months:

Cross Match:

Neg – 0/ Pos <5% - 1 / Pos 5-20% - 2 / Pos >20% - 3

HLA:

Nil -0

Single Ag(A or B) -1

Single Ag +DR -2 / Haplo – 3

3 Ag match – 4

Full – 5. If more than 1 Ag matches to fill below details:

- A: 1/2
- B:1/2
- DR:1/2
- DQ:1/2

Native Kidney Disease

1. Unknown
2. FSGS

3. Diabetic Nephropathy
4. Ig A Nephropathy
5. Reflux/Obstructive Nephropathy
6. Membranous nephropathy
7. Mesangial Proliferative GN
8. Others: Cresentric GN, Lupus Nephritis, Vasculitis

Induction: Induction: Nil – 0 / Simulect – 1 / ATG – 2 / Daclizumab – 3 / Others – 4

Warm Ischemia Time (min):

Cold Ischemia Time (min):

Blood transfusion before transplant:

1. Nil
2. ≤2pints
3. >2≤5 pints
4. >5pints

No: of Anti-hypertensive drugs before transplant:

1. Nil drugs
2. ≤2 drugs
3. >2 drugs

No: of Anti-hypertensive drugs after transplant with CNI:

1. Nil drugs
2. ≤2 drugs
3. >2 drugs

Type of Immunosuppression:

1. Prednisolone: No -0 / Yes -1
2. Cyclosporin: No -0 / Yes -1
3. Tacrolimus: No -0 / Yes -1
4. Azathioprine: No -0 / Yes -1
5. MMF: No -0 / Yes -1
6. Sirolimus: No -0 / Yes -1
7. Everolimus: No -0 / Yes -1

Duration of follow up (Last Visit) in Months:

Dose of Immunosuppresion (AUC) at various time points:

	0month	2month	4month	6month	12month
Tacrolimus					
Cyclosporine					
Cumm Steroids					

CLINICAL DATA

Anthropometric Measurements of recipient:

Ht: cms	Ht: cms	WT: Kg	BMI
Pre-Tx Wt0/BMI0			
2month Wt2/BMI2			
4month Wt4/BMI4			
6month Wt6/BMI6			
9-12mth t12/BMI12			

Blood Pressure Monitoring

Office BP at the time of CABP

Date	SBP1	SBP2	SBP3	DBP1	DBP2	DBP3
2^{nd} mth						
4^{th} mth						
6^{th} mth						
9^{th}-12^{th}mth						

CABP: DT-Day time, NT-Night Time

Date	24hr Syst	24hr Dias	DT Sys	DT Dias	NT Sys	NT Dias	Ratio of NSBP:NDBP	Ratio of DSBP:DDBP
2^{nd} mth								
4^{th} mth								
6^{th} mth								
9^{th}-12^{th}mth								

Normal Circadian Rhythm: Sleep: Awake Ratio :> 0.92(SBP) and >0.9(DBP)

1. Yes
2. No

Dipper/Non-Dipper Status

1. Dipper(0.8-0.9)
2. Non-Dipper(0.9-1)
3. Inverted Dipper(>1)

Left ventricular Mass

	LVM	LVMI	ΔLVMI
Pre-Transplant			
9^{th} Post Tx			

Investigation Profile at the time of CABP

	Sr.Creat	eGFR	Sr.Alb	24hr.Prot	Lipids
Pre-Tx					
2nd mth					
4th mth					
6th mth					
9-12th mth					
Last Visit					

No. of Rejection episodes:

Num				
Date				
Acute / chronic				
Vascular / cellular				
Type				
Rx No-0 MePred3 -1 ATG -2 OKT3-3				
Response Nil -0 / Parital-1 / Full -2				

BIBLIOGRAPHY

1. Kidney and Urinary Tract. Volume II; Eighth Edition, Robert Schrier.
2. Hypertension. A Companion to Brenner and Rector's The Kidney. Second Edition. Suzanne Orail and Michael A. Weber.
3. Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365:217–23.
4. Gupta R. Trends in hypertensive epidemiology in India. J Hum Hypertens. 2004; 18:73-78.
5. Mohan JC. Prevalence, awareness, treatment, control, and risk factors of hypertension in India and its neighborhood: Newer data and older perspective. Indian Heart J.2006;58:7-9
6. Hypertension Study Group. Prevalence, awareness, treatment and control of hypertension among the elderly in Bangladesh and India: a multicentre study. Bulletin of the World Health Organization 2001; 79:490-500
7. Thankappan KR, Sivasankaran S, Khader SA, Padmanabhan PG, Sarma PS, Mini GK et.al. Prevalence, Correlates, Awareness, Treatment, and Control of Hypertension in Kumarakom, Kerala. Baseline Results of a Community-Based Intervention Program. Indian Heart J2006; 58:28-33.
8. Bloch MJ. Analysis of recent papers in hypertension: the increasing burden of hypertension in the United States—65 million and counting. J Clin Hypertens (Greenwich) 2004; 6:722–3.

9. Greenlund KJ, Croft JB, Mensah GA. Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. Arch Intern Med 2004; 164:2113–8.
10. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42:1206–52.
11. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med 2001;345:479–86.
12. Burt VL, Culter JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991 [published erratum appears in Hypertension 1996; 27:1192]. Hypertension 1995; 26:60–9.
13. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995; 25:305–13.
14. United States Renal Data System: USRDS 1997–2004 Annual Data Report. U.S. Department of Health and Human Services. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, August 1997,1998,1999,2000.
15. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 2003;139: 244–52.

16. Smith JP, Lewis JB. Hypertension management: special considerations in chronic kidney disease patients. Curr Hypertens Rep 2004;6:462–8.
17. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J: A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. Transplantation 73:775-782, 2002
18. Fernandez-Fresnedo G, Palomar R, Escallada R, Martin de Francisco AL, Cotorruelo JG, Zubimendi JA, Sanz de Castro S, Ruiz JC, Rodrigo E, Arias M: Hypertension and long-term renal allograft survival: Effect of early glomerular filtration rate. Nephrol Dial Transplant 16:105-109, 2001 (suppl 1)
19. Mange KC, Cizman B, Joffe M, Feldman HI: Arterial hypertension and renal allograft survival. JAMA 283:633-638, 2000
20. Zayas CF, Guasch A: Early glomerular dysfunction in human renal allografts. Kidney Int 60:1938-1947, 2001
21. Brazy PC, Pirsch JD, Belzer FO: Factors affecting renal allograft function in long-term recipients. Am J Kidney Dis 19:558-566, 1992
22. National Kidney Foundation. K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. Am J Kidney Dis. 2004 May; 43(5 Suppl 1):S1-290. 2003
23. European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003; 21:1011–53.
24. Touyz RM, Campbell N, Logan A, et al. The 2004 Canadian recommendations for the management of hypertension: part III—lifestyle modifications to prevent and control hypertension. Can J Cardiol 2004; 20:55–9.

25. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; 21:1983–92.
26. Williams B, Poulter NR, Brown MJ, et al. Guidelines for management of hypertension: report of the Fourth Working Party of the British Hypertension Society, 2004- BHS IV. J Hum Hypertens 2004; 18:139–85.
27. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997; 157:2413–46.
28. Vasan RS, Larson MG, Leip EP, et al. Impact of high normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345:1291–7.
29. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. JAMA 2002; 287:1003–10.
30. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114:555–76.
31. Vasan RS, Larson MG, Leip EP, et al. Assessment of frequency of progression to hypertensive in non-hypertensive participants in the Framingham Heart Study. Lancet. 2001 ;358: 1682-1686.
32. Circadian blood pressure: Clinical implications based on the pathophysiology of its variability. AJ Peixoto and WB White. Kidney International (2007) 71, 855–860. doi:10.1038/sj.ki.5002130;

33. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978; 1: 795–797.

34. Cranston WI. Diurnal variations in plasma volume in normal and hypertensive subjects. Am Heart J 1964; 68: 427–428.

35. Pickering TG, James GD. Determinants and consequences of the diurnal rhythm of blood pressure. Am J Hypertens 1993; 6: 166S–169S.

36. James GD, Pickering TG. The influence of behavioral factors on the daily variation of blood pressure. Am J Hypertens 1993; 6: 170S–173S.

37. Adrian Covic, MD, PhD, and David J.A. Goldsmith: Ambulatory Blood Pressure Measurement in the Renal Patient. Current Hypertension Reports 2002, 4:369–376

38. Lurbe E, Redon J, Kesani A et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Eng J Med 2002; 347: 797–805.

39. Uzu T, Ishikawa K, Fujii T et al. Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. Circulation 1997; 96: 1859–1862.

40. Wilson DK, Sica DA, Miller SB. Effects of potassium on blood pressure in salt-sensitive and salt-resistant adolescents. Hypertension 1999; 34: 181–186.

41. Narkiewicz K, Winnicki M, Schroeder K et al. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. Hypertension 2002; 39: 168–172.

42. Carvalho MJ, van Den Meiracker AH, Boomsma F et al. Diurnal blood pressure variation in progressive autonomic failure. Hypertension 2000; 35: 892–897.

43. Portaluppi F, Bagni B, degli Uberti E et al. Circadian rhythms of atrial natriuretic peptide, rennin, aldosterone, cortisol, blood pressure and heart rate in normal and hypertensive subjects. J Hypertens 1990; 8: 85–95.

44. Farmer CK, Goldsmith DJ, Cox J et al. An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. Nephrol Dial Transplant 1997; 12: 2301–2307.

45. Fagugli RM, Reboldi G, Quintaliani G, *et al.*: Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis* 2001, 38:371–37

46. Narita I, Okada M, Omori S, *et al.*: The circadian blood pressure rhythm in non-diabetic hemodialysis patients. *Hypertens Res* 2001, 24:111–117.

47. Converse RLJ, Jacobsen TN, Toto RD, *et al.*: Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992, 327:1912–1918.

48. Vita G, Princi P, Savica V, *et al.*: Uremic autonomic dysfunction evaluated by pattern recognition analysis. *Clin Nephrol* 1991, 36:290–293

49. Thompson AM and Pickering TG: The role of ambulatory blood pressure monitoring in chronic and end-stage renal disease. Kidney International (2006) 70, 1000–1007.

50. Fagugli RM, Reboldi G, Quintaliani G, *et al.*: Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis* 2001, 38:371–376.

51. McGregor DO, Buttimore AL, Nicholls MG, Lynn KL. Ambulatory blood pressure monitoring in patients receiving long, slow home haemodialysis. Nephrol Dial Transplant 1999; 14: 2676–2679.
52. Santos SF, Mendes RB, Santos CA et al. Profile of interdialytic blood pressure in hemodialysis patients. Am J Nephrol 2003; 23: 96–105.
53. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993; 328: 303–307.
54. Converse Jr RL, Jacobsen TN, Toto RD et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 1992; 327: 1912–1918.
55. Sherwood A, Steffen PR, Blumenthal JA et al. Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens 2002; 15: 111–118.
56. O'Shea JC, Murphy MB. Nocturnal blood pressure dipping: a consequence of diurnal physical activity blipping? Am J Hypertens 2000; 13: 601–606.
57. Pedulla M, Silvestri R, Lasco A et al. Sleep structure in essential hypertensive patients: differences between dippers and non-dippers. Blood Press 1995; 4: 232–23
58. Kuhlmann U, Becker HF, Birkhahn M et al. Sleep-apnea in patients with end-stage renal disease and objective results. Clin Nephrol 2000; 53: 460–466.
59. Hermida RC, Calvo C, Ayala DE et al. Relationship between physical activity and blood pressure in dipper and non-dipper hypertensive patients. J Hypertens 2002; 20: 1097–1104.
60. Padiyar A, Rahman M. Ambulatory blood pressure monitoring: an argument for wider clinical use. Cleve Clin J Med 2007;74(11):831–8.

61. Amar J, Vernier I, Rossingol E, Lenfant V, Conte JJ, Chamontin B. Influnce of nycthemeral blood pressure pattern in treated hypertensive patients on hemodialysis. Kidney Int. 1997; 51:1861-1863
62. Gatzka CD, Schobel HP, Klingbel AU et.al Normalization of circadian blood pressure profiles after renal transplantation. Transplantation 1995; 59: 1270-1274
63. Farmer CKT, Goldsmith DJA, Cox J et.al An investigation of the effect of advancing uremia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. Nephrol Dial Transplant 1997; 12:2301-2307
64. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J: A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: Evidence for improved allograft survival at five years. Transplantation 73:775-782, 2002
65. Opelz G, Wujciak T, Ritz E: Association of chronic kidney graft failure with recipient blood pressure. Collaborative Transplant Study. Kidney Int 53:217-222, 1998
66. Brazy PC, Pirsch JD, Belzer FO: Factors affecting renal allograft function in long-term recipients. Am J Kidney Dis 19:558-566, 1992
67. Fernandez-Fresnedo G, Palomar R, Escallada R, Martin de Francisco AL, Cotorruelo JG, Zubimendi JA, Sanz de Castro S, Ruiz JC, Rodrigo E, Arias M: Hypertension and long-term renal allograft survival: Effect of early glomerular filtration rate. Nephrol Dial Transplant 16:105-109, 2001 (suppl 1)
68. Mange KC, Cizman B, Joffe M, Feldman HI: Arterial hypertension and renal allograft survival. JAMA 283:633-638, 2000

69. Zayas CF, Guasch A: Early glomerular dysfunction in human renal allografts. Kidney Int 60:1938-1947, 2001

70. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, Roth D, Scandling JD, Singer GG: Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol 11:S1-S86, 2000 (suppl 15)

71. Brazy PC, Pirsch JD, Belzer FO: Factors affecting renal allograft function in long-term recipients. Am J Kidney Dis 19:558-566, 1992

72. Fernandez-Fresnedo G, Palomar R, Escallada R, Martin de Francisco AL, Cotorruelo JG, Zubimendi JA, Sanz de Castro S, Ruiz JC, Rodrigo E, Arias M: Hypertension and long-term renal allograft survival: Effect of early glomerular filtration rate. Nephrol Dial Transplant 16:105-109, 2001 (suppl 1)

73. Mange KC, Cizman B, Joffe M, Feldman HI: Arterial hypertension and renal allograft survival. JAMA 283:633-638, 2000

74. Zayas CF, Guasch A: Early glomerular dysfunction in human renal allografts. Kidney Int 60:1938-1947, 2001

75. Brem AS. Insights into glucocorticoid-associated hypertension. Am J Kidney Dis 2001; 37:1–10. 8.

76. Veenstra DL, Best JH, Hornberger J, et al. Incidence and long-term cost of steroid-related side effects after renal transplantation. Am J Kidney Dis 1999; 33:829–39.

77. Luke RG: Pathophysiology and treatment of posttransplant hypertension. J Am Soc Nephrol 1991 ;2(Suppl 1j:S37-S44.

78. Curtis JJ: Cyclosporine and Posttransplant Hypertension. J. Am. Soc. Nephrol. 1991; 2:537-544

79. Curtis JJ: Cyclosporine and hypertension. Clin Transplant 1990:4:337-340.

80. Curtis JJ, Galla JH, Kotchen TA, Lucas B, McRoberts JW, Luke RG: Prevalence of hypertension in a renal transplant population on alternate-day steroid therapy. Clin Nephrol 1976; 5:123-121.

81. Hariharan, Schroeder TJ, Weiskittel P, Alexander JW, First MR: Prednisone withdrawal in HLA identical and one haplotype-matched live related donor and cadaver renal transplant recipients. Kidney Int 1993:44[Suppl 43]:S30-S35.

82. Curtis JJ. Posttransplantation hypertension. Transplant Proc 1998; 30:2009–11.

83. Morales JM, Andres A, Rengel M, Rodicio JL. Influence of cyclosporine, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. Nephrol Dial Transplant 2001;16 Suppl 1:121–4.

84. Koomans HA, Ligtenberg G. Mechanisms and consequences of arterial hypertension after renal transplantation.Transplantation 2001;72(6 Suppl):S9–12.

85. Textor SC, Canzanello VJ, Taler SJ, et al. Cyclosporine induced hypertension after transplantation. Mayo Clin Proc 1994; 69:1182–93.

86. Perez Fontan M, Rodriguez-Carmona A, Garcia Falcon T, et al. Early immunologic and nonimmunologic predictors of arterial hypertension after renal transplantation. Am J Kidney Dis 1999; 33:21–8.

87. Budde K, Waiser J, Fritsche L, et al. Hypertension in patients after renal transplantation. Transplant Proc 1997; 29:209–11.

88. Moss NG, Powell SL, Falk WF: Intravenous cyclosporine activates afferent and efferent renal nerves and causes sodium retention in innervated kidneys in rats. Proc Natl Acad Scm USA 1985; 82:8222-8226.

89. June CH, Thompson CB, Kennedy MS. Nims J, Thomas ED: Profound hypomagnesemia and renal magnesium wasting associated with the use of cyclosporine for marrow transplantation. Transplantation 1 985; 39:620-624.

90. Kidney Transplantation, Principles and Practice. 5th Edition; Peter J. Morris

91. Thompson JF, Wood RFM, Taylor HM, et al:Control of hypertension after renal transplantation by embolization of host kidneys. Lancet 1984; 2:424-427.

92. Guidi E, Blanchi G, Dallosta V, et al. : Influence of familial hypertension of the donor on the blood pressure and antihypertensive therapy of kidney graft recipients. Nephron 1982; 30: 318-323.

93. Pickering TG, Gerin W, Schwartz AR. What is the white-coat effect and how should it be measured? Blood Press Monit 2002; 7:293-300.

94. O'Brien E, Asmar R, Beilin L, et al. European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003; 21:821–48.

95. Paratia G and Valentinia M. Do we need out-of-office blood pressure in every patient? Current Opinion in Cardiology 2007, 22:321–328

96. Turner MJ, Baker AB, Kam PC. Effects of systematic errors in blood pressure measurements on the diagnosis of hypertension. Blood Press Monit 2004; 9:249–53.

97. Thavarajah S, White WB, Mansoor GA. Terminal digit bias in a specialty hypertension faculty practice. J Hum Hypertens 2003; 17:819–22.

98. Parati G, Stergiou GS. Self measured and ambulatory blood pressure in assessing the 'white-coat' phenomenon. J Hypertens 2003; 21:677–82.

99. Johnson KA, Partsch DJ, Rippole LL,McVey DM. Reliability of self-reported blood pressure measurements. Arch Intern Med 1999; 159:2689–93.

100. Staessen JA, Den Hond E, Celis H, et al. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. JAMA 2004; 291:955–64.

101. Staessen JA, Thijs L. Development of diagnostic thresholds for automated self-measurement of blood pressure in adults. First International Consensus Conference on Blood Pressure Self-Measurement. Blood Press Monit 2000; 5:101–9.

102. Mansoor GA, White WB. Self-measured home blood pressure in predicting ambulatory hypertension. Am J Hypertens 2004; 17:1017–22

103. Divison JA, Sanchis C, Artigao LM, et al. Home-based selfmeasurement of blood pressure: a proposal using new reference values (the PURAS study). Blood Press Monit 2004; 9:211–8.

104. Imai Y, Poncelet P, DeBuyzere M, et al. Prognostic significance of self-measurements of blood pressure. Blood Press Monit 2000; 5:137–43.

105. Ohkubo T, Imai Y, Tsuji I, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure

measurement: a population-based observation in Ohasama, Japan. J Hypertens 1998; 16:971–5.

106. Imai Y, Hozawa A, Ohkubo T, et al. Predictive values of automated blood pressure measurement: what can we learn from the Japanese population - the Ohasama study. Blood Press Monit 2001; 6:335–9.

107. Mengden T, Chamontin B, Phong Chau NG, Gamiz JLP, Chanudet X, and the participants of the First International Consensus Conference on Blood Pressure Self-Measurement. User procedure for self-measurement of blood pressure. Blood Press Monit 2000; 5:111–129.

108. Imai Y, Nishiyama A, Sekino M, Aihara A, Kikuya M, Ohkubo T, et al. Characteristics of blood pressure measured at home in the morning and in the evening; the Ohasama study. J Hypertens 1999; 101: 889–89

109. Stergiou GS, Skeva II, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? J Hypertens 1998; 16:725–731.

110. Owens P, Atkins N, O'Brien E. Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. Hypertension 1999; 34: 267–272.

111. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers [letter]. Lancet 1988; ii:397.

112. Owens P, Lyons S, O'Brien E. Ambulatory blood pressure in the hypertensive population: patterns and prevalence of hypertensive subforms. J Hypertens 1998; 16:1735–1743.

113. White WB. Ambulatory blood-pressure monitoring in clinical practice. N Engl J Med 2003; 348:2377–8.

114. Ohkubo T, Imai Y, Tsuji I, Nagai K, Ito S, Satoh H, Hisamichi S. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion: the Ohasama Study. Hypertension 1998; 32:255–259.

115. Jacobi et.al; Prospective Analysis of the value of 24-hour Ambulatory Blood pressure on Renal Function after Kidney Transplantation. Transplantation Vol. 70, 819–827, No. 5, September 15, 2000.

116. Hayadar et.al. Insights from Ambulatory Blood pressure monitoring: Diagnosis of Hypertension and Diurnal Blood pressure in Renal Transplant Recipients. Transplanatation; Vol. 77, 849–853, No. 6, March 27, 2004.

117. Lingens N, Dobos E, Witte K, et al. Twenty-four-hour ambulatory blood pressure profiles in pediatric patients after renal transplantation. Pediatr Nephrol 1997; 11(1): 23.

118. Kooman JP, Christiaans MH, Boots JM, et al. A comparison between office and ambulatory blood pressure measurements in renal transplant patients with chronic transplant nephropathy. Am J Kidney Dis 2001; 37(6): 1170.

119. Opelz G, Wujciak T, Ritz E, for the Collaborative Transplant Study. Association of chronic kidney graft failure with recipient blood pressure. Kidney Int 1998; 53: 217.

120. White WB, Schulman P, Mc Cabe EJ, Dey HM. Average daily blood pressure, not office blood pressure, determines cardiac function in patients with hypertension. JAMA 1989; 261: 873.

121. Verdecchia P, Schillaci G, Guerrieri M. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990; 81: 528.

122. Giaconi S, Levanti C, Fommei E, et al. Microalbuminuria and casual and ambulatory blood pressure monitoring in normotensives and in patients with borderline and mild essential hypertension. Am J Hypertens 1989; 2: 259.

123. Redon J, Liao Y, Lozano JV, Miralles A, Pascual JM, Cooper RS. Ambulatory blood pressure and microalbuminuria in essential hypertension: role of circadian variability. J Hypertens 1994; 12: 947.

124. Asmar RG, Brunel PC, Painer BM, Cacolley PJ, Safar ME. Arterial distensibility and ambulatory blood pressure monitoring in essential hypertension. Am J Cardiol 1988; 61:1066.

125. Opelz G, Wujciak T, Ritz E, for the Collaborative Transplant Study. Association of chronic kidney graft failure with recipient blood pressure. Kidney Int 1998; 53: 217.

126. Calzolari A, Giordano U, Matteucci MC, et al. Hypertension in young patients after renal transplantation. Ambulatory blood pressure monitoring versus casual blood pressure. Am J Hypertens 1998; 11: 497.

127. Tine Willum Hansen, Jørgen Jeppesen, Susanne Rasmussen, Hans Ibsen, and Christian Torp-Pedersen. Ambulatory Blood Pressure Monitoring and Risk of Cardiovascular Disease: A Population Based Study. Am J Hypertens 2006; 19: 243–250.

128. S Prakash et. al Assessment of Hypertension Control in Chronic Kidney Disease Patients by Ambulatory Blood Pressure Monitoring. JAPI; VOL. 53, September 2005.

129. Stergiou GS et.al. Home Blood Pressure Is as Reliable as Ambulatory Blood Pressure in Predicting Target-Organ Damage in Hypertension. AJH 2007; 20:616–621.

130. Verdecchia et.al. Circadian Blood Pressure Changes and Left Ventricular Hypertrophy in Essential Hypertension. Circulation Vol 81, No 2, February 1990

131. Devereux RB, Pickering TG, Harshfield GA, Kleinert HD, Denby L, Clark L, Pregibon D, Jason M, Kleinert B, Borer JS, Laragh JH: Left ventricular hypertrophy in patients with hypertension: Importance of blood pressure response to regularly recurring stress. Circulation 1983;68:470-476

132. Drayer JIM, Weber MA, DeYoung JL: BP as a determinant of cardiac left ventricular muscle mass. Arch Intern Med 1983; 143:90-92

133. Rowlands DB, Glover DR, Ireland MA, McLeay RAB, Stallard TJ, Watson RDS, Littler WA: Assessment of left ventricular mass and its response to antihypertensive treatment. Lancet 1982;1:467-470

134. Soraia R.C, Ferreira,Valdir A, Moises, Agostinho Tavares and Alvaro Pacheco-Silva. Cardiovascular Effects Of Successful Renal Transplantation: A 1-Year Sequential Study Of Left Ventricular Morphology And Function, And 24-Hour Blood Pressure Profile. Transplantation.Vol. 74, 1580–1587, No. 11, December 15, 2002

135. Balal M et.al Daily blood pressure control is not sufficient to regress cardiac hypertrophy and dysfunction: A bi-ventricular tissue Doppler echocardiographic study NEPHROLOGY 2007; 12, 140–146

136. Cuspidi et.al. How reliable is isolated clinical hypertension defined by a single 24-hr ambulatory blood pressure monitoring? Journal of Hypertension. 2007; 25,315-320

137. Flack JM et.al Prevention of Hypertension and Its Complications: Theoretical Basis and Guidelines for Treatment. J Am Soc Nephrol 14: S92–S98, 2003

138. Jokinitty et.al. Pulse pressure is the best predictor of future left ventricular mass and change in left ventricular mass: 10years of follow up. Journal of Hypertension 2001, 19: 2047-2054

139. Fernandez-Fresnedo G, Escallada R, et al. Association between pulse pressure and cardiovascular disease in renal transplant patients. Am J Transplant 2005; 5: 394.

140. Yves F. C. Vanrenterghem, Kathleen Claes, Giuseppe Montagnino, Steffen Fieuws, Bart Maes, Margarita Villa,2,4 and Claudio Ponticelli. Risk Factors for Cardiovascular Events After Successful Renal Transplantation. Transplantation 2008;85: 209–216

141. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: A significant independent risk factor for graft failure and patient death. Transplantation 2002; 73: 70.

142. Howard RJ, Thai VB, Patton PR, et al. Obesity does not portend a bad outcome for kidney transplant recipients. Transplantation 2002; 73: 53.

143. Montagnino G, Tarantino A, Segoloni G, et al. Long-term results of a randomized study comparing three immunosuppressive schedules with cyclosporine in cadaveric kidney transplantation. J Am Soc Nephrol 2001; 12: 2163.

144. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003; 3: 178.

145. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296.

146. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004; 351: 1285.

147. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003; 75: 1291.

148. Kasiske BL, Guijarro C, Massy ZA, et al. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7: 158.

149. Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and mortality in incident hemodialysis patients. Kidney Int 2004; 65: 626.

150. Winkelmayer WC, Chandraker A, Brookhart MA, et al. Prospective study of anemia and long-term outcomes in kidney transplant recipients. Nephrol Dial Transplant 2006; 21: 3559.

151. Molnar MZ, Czira M, Ambrus C, et al. Anemia is associated with mortality in kidney-transplanted patients-A prospective cohort study. AmJ Transplant 2007; 7: 818.

152. Muiesan et.al Structural Association between carotid artery and left ventricle in a general population in Northern Italy: The Vobarno Study. Journal of Hypertension 1998. 16:1805-1812

153. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1. Blood pressure measurement in humans. Circulation 2005; 111:697–716.

154. Staessen JA, Bieniaszewski L, O'Brien ET, et al. Special feature: what is a normal blood pressure in ambulatory monitoring? Nephrol Dial Transplant 1996;11:241.

155. Staessen JA, Bieniaszewski L, O'Brien E, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The "Ad Hoc" Working Group. Hypertension 1997;29:30.

156. Narita et.al The circardian BP rhythm in non-diabetic HD patients. Hypertens Res 2001,38:371-376

157. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32(5 suppl 3): S112.

158. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 2000; 35(4 suppl 1): S117.

159. Soraia R. C. Ferreira, Valdia A Moises, Agostinho Tavares, and Alvaro Pacheco-Silva. Cardiovascular effects of successful renal transplantation: A 1-year sequential function and 24-hour blood pressure profile. Transplantation. 74, 1580–1587, No. 11, December 15, 2002

160. Devereux RB, Lutas EM, Casale PN. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol 1984; 4: 1222.

161. Adrian Covic, Liviu Segall, and David J. A. Goldsmith. Ambulatory Blood Pressure Monitoring In Renal Transplantation: Should ABPM Be Routinely Performed In Renal Transplant Patients? Transplantation Vol. 76, No. 1; December 15, 2003

162. Gerry Ligtenberg, Ronald J. Hené, Peter J. Blankestijn, and Hein A. Koomans. Cardiovascular Risk Factors in Renal Transplant Patients: Cyclosporin A Versus Tacrolimus. J Am Soc Nephrol 12: 368–373, 2001

163. José M. Morales, Amado Andres, Manuel Rengel and José L. Rodicio. Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. Nephrol Dial Transplant (2001) 16: 121-124

164. Adrian Covic, Paul Gusbeth-Tatomir, Nicoleta Mardare, Irina Buhaescu, and David J.A. Goldsmith. Dynamics of the Circadian Blood Pressure Profiles after Renal Transplantation. Transplantation 2005;80: 1168–1173

165. Faria MD, Nunes JP, Ferraz JM, et al. 24-hour blood pressure profile early after renal transplantation. Rev Port Cardiol 1995;14:227.

166. Gatzka CD, Schobel HP, Klingbeil AU, et al. Normalization of circadian blood pressure profiles after renal transplantation. Transplantation 1995;59:1270.

167. Lipkin GW, Tucker B, Giles M, Raine AE. Ambulatory blood pressure and left ventricular mass in cyclosporin- and non-cyclosporin-treated renal transplant recipients, J Hypertens 1993;11:439